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(73)专利权人 美利坚合众国-由健康及人类服务部部长代表
地址 美国马里兰州
(72)发明人 P·L·柯林斯 U·J·巴克霍尔兹 C·罗格
(74)专利代理机构 北京坤瑞律师事务所 11494
专利代理师 封新琴
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审查员 田颖

权利要求书3页 说明书117页
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(54)发明名称

提供一系列减毒表型的在M2-2 ORF中具有突变的重组呼吸道合胞病毒株

(57)摘要

本文提供新型重组呼吸道合胞病毒(RSV),其具有在M2-2开放阅读框中包含干扰M2-2蛋白表达的突变的减毒表型。M2-2突变可与在其他基因座的突变组合出现。使用本文所述的方法,提供突变组合以实现预期的减毒水平。本文所述的重组RSV株适于用作活的减毒RSV疫苗。还提供了所述病毒的多核苷酸序列,以及用于产生和使用所述病毒的方法。

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1.重组呼吸道合胞病毒(RSV),其通过对重组RSV基因组的一种或多种修饰减毒,其中所述一种或多种修饰包括:

(a)在M2-2开放阅读框(ORF)中对应SEQ ID NO:1的位置8189-8429的241个核苷酸缺失的缺失组合在对应SEQ ID NO:1的位置T8161、T8167和T8179的核苷酸突变("ΔM2-2");和

对应SEQ ID NO:1的位置4499-4610的112个核苷酸的缺失组合在对应SEQ ID NO:1的C4489T、C4492T、A4495T、A4497G和G4498A的位置的核苷酸突变("6120")。

2.根据权利要求1所述的重组RSV,其中所述一种或多种修饰进一步包括编码RSV的N蛋白中的V267I、F蛋白中的E218A和T523I和L蛋白中的C319Y和H1690Y的氨基酸取代的核苷酸突变("cp")。

3.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括在RSV的L蛋白中引入Y1321K取代的核苷酸突变,且其中所述L蛋白包括S1313残基,其中编码Y1321K取代和S1313残基的密码子分别是AAA和TCA密码子("1030s")。

4.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括编码RSV的NS2蛋白中的氨基酸取代K51R的核苷酸突变("NS2")。

5.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括编码RSV的N蛋白中的氨基酸取代T24A的核苷酸突变("N")。

6.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括编码RSV的NS2蛋白中的K51R和N蛋白中的T24A的氨基酸取代的核苷酸突变("NS2/N")。

7.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括在SH ORF中对应SEQ ID NO:1的位置4198-4616的419个核苷酸的缺失("ΔSH")。

8.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括将编码RSV的G蛋白的核苷酸序列替换为编码来自临床分离株A/Maryland/001/11的G蛋白的相应密码子优化的核苷酸序列。

9.根据权利要求8所述的重组RSV,其中所述编码来自临床分离株A/Maryland/001/11的G蛋白的密码子优化的核苷酸序列包含对应于SEQ ID NO:8的核苷酸序列(G001BB)。

10.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为SEQ ID NO:9中所述的相应密码子优化的核苷酸序列(FBB)。

11.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为编码来自临床分离物A/Maryland/001/11的F蛋白的SEQ ID NO:10所述的相应核苷酸序列(F001)。

12.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为编码来自临床分离株A/Maryland/001/11的F蛋白的相应密码子优化的核苷酸序列。

13.根据权利要求12所述的重组RSV,其中编码来自临床分离株A/Maryland/001/11的F蛋白的密码子优化的核苷酸序列包含对应于SEQ ID NO:11的核苷酸序列(F001BB)。

14.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰还包括在RSV的F蛋白中编码氨基酸取代K66E和Q101P的核苷酸突变("HEK")。

15.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰还包括编码RSV的F蛋

白中的氨基酸取代E218A和T523I的核苷酸突变(F cp取代)。

16.根据权利要求1或2所述的重组RSV,其中所述一种或多种修饰进一步包括逆转编码RSV基因组中G和F蛋白的基因的顺序。

17.根据权利要求1所述的重组RSV,其中所述一种或多种修饰包括选自以下任一项的突变的组合或由其组成:

6120/ΔM2-2、6120/cp/ΔM2-2、6120/ΔM2-2/1030s、6120/NS2/N/ΔM2-2、6120/G001BB/FBB/ΔM2-2、6120/FBB/G001BB/ΔM2-2、6120/G001BB/F/ΔM2-2、6120/G/FBB/ΔM2-2、6120/G/FBBHEK/ΔM2-2、6120/G/FBBcpHEK/ΔM2-2、6120/FBB/G/ΔM2-2、6120/G001BB/F001BB/ΔM2-2、6120/NS2/ΔM2-2或6120/N/ΔM2-2。

18.根据权利要求1或2所述的重组RSV,其中所述重组RSV基因组包括所述一种或多种修饰和对应于根据SEQ ID NO:5的正义序列的核苷酸序列。

19.根据权利要求1或2所述的重组RSV,其中所述重组RSV基因组是含有所述一种或多种修饰的D46基因组。

20.根据权利要求1所述的重组RSV,其中所述重组RSV基因组包括:

6120、cp和ΔM2-2突变,和对应于根据SEQ ID NO:17(LID/cp/ΔM2-2序列)的正义序列的核苷酸序列。

21.根据权利要求1所述的重组RSV,其中所述重组RSV基因组包括:

6120、ΔM2-2和1030s突变,和对应于根据SEQ ID NO:16(LID/ΔM2-2/1030s序列)的正义序列的核苷酸序列。

22.根据权利要求1所述的重组RSV,其中所述重组RSV基因组的核苷酸序列包括对应于下述任一项所述的正义序列的核苷酸序列或由其组成:SEQ ID NO:5、SEQ ID NO:17。

23.根据权利要求1所述的重组RSV,其中所述重组RSV基因组的核苷酸序列包括对应于SEQ ID NO:16的正义序列的核苷酸序列或由其组成。

24.根据权利要求1或2所述的重组RSV,其中所述RSV是亚型A RSV。

25.根据权利要求1或2所述的重组RSV,其中所述RSV是亚型B RSV。

26.根据权利要求1或2所述的重组RSV,其中所述RSV是感染性、减毒和自我复制的。

27.一种分离的多核苷酸分子,其包含权利要求1-26任一项的重组RSV基因组的核苷酸序列,或所述RSV基因组的反基因组cDNA或RNA序列。

28.一种载体,其包含权利要求27的多核苷酸分子。

29.一种细胞,其包含权利要求27的多核苷酸分子或权利要求28的载体。

30.一种产生重组RSV的方法,包括:

使用权利要求28所述的载体转染许可细胞培养物;

温育所述细胞培养物足够的时间以允许病毒复制;和

纯化所述复制的重组RSV。

31.通过权利要求30所述的方法产生的重组RSV。

32.一种药物组合物,其包含权利要求1-26和31中任一项所述的重组RSV。

33.权利要求32所述的药物组合物在制备用于在受试者中引发对RSV的免疫应答的药物中的用途。

34.根据权利要求33所述的用途,其中所述免疫应答是保护性免疫应答。

35.根据权利要求33或34所述的用途,其中所述药物组合物鼻内施用。

36.根据权利要求33或34所述的用途,其中所述RSV经由注射、气溶胶递送、鼻喷雾或鼻滴施用。

37.根据权利要求33或34所述的用途,其中所述受试者是人。

38.根据权利要求33或34所述的用途,其中所述受试者为1至6月龄。

39.根据权利要求33或34所述的用途,其中所述受试者对于RSV为血清阴性。

40.权利要求1-26和权利要求31中任一项的重组RSV在制备用于在受试者中引发对RSV的免疫应答的药物中的用途。

41.权利要求1-26和权利要求31中任一项所述的重组RSV、权利要求27所述的多核苷酸分子、权利要求28所述的载体或权利要求29所述的细胞在制备用于在受试者中引发对RSV的免疫应答的药物中的用途。

提供一系列减毒表型的在M2-2 ORF中具有突变的重组呼吸道合胞病毒株

[0001] 相关申请

[0002] 本申请要求保护2015年12月11日提交的美国临时申请号62/266,199的优先权,其以其整体通过引用并入。

[0003] 领域

[0004] 本文公开的主题涉及呼吸道合胞病毒(RSV)及其适合用作疫苗的减毒突变株。

[0005] 背景

[0006] 人类呼吸道合胞病毒(RSV)在生命早期几乎感染了全世界每个人,并导致相当大的死亡率和发病率。仅在美国,RSV每年就有75,000-125,000例住院治疗,保守估计表明RSV在全世界每年导致6400万儿童感染和160,000或更多儿科死亡。RSV的另一个值得注意的特征是,婴儿期的严重感染经常在之后有持续的气道功能障碍,包括气道反应性的倾向,其在某些个体中持续多年并且可以延及青春期及以后。RSV感染加剧哮喘,并可能与哮喘开始有关。

[0007] RSV是副粘病毒科的成员,因此是包膜病毒,其在细胞质中复制并通过在宿主细胞质膜上出芽而成熟。RSV的基因组是15.2千碱基的RNA的单个、负义链,其通过顺序终止-起始机制由病毒聚合酶转录成10个mRNA,所述终止-起始机制在基因组的3'末端处的单个病毒启动子处起始。每个mRNA编码单个主要蛋白质,除了M2mRNA具有两个重叠的开放阅读框(ORF),其编码两个独立的蛋白质M2-1和M2-2。11种RSV蛋白为:RNA结合核蛋白(N),磷蛋白(P),大聚合酶蛋白(L),附着糖蛋白(G),融合蛋白(F),小疏水性(SH)表面糖蛋白,内部基质蛋白(M),两种非结构蛋白NS1和NS2,以及M2-1和M2-2蛋白。RSV基因顺序为:3'-NS1-NS2-N-P-M-SH-G-F-M2-L。每个基因的侧翼都是称为基因-起始(GS)信号的短保守转录信号以及基因末端(GE)信号,所述基因-起始(GS)信号存在于每个基因的上游末端,并参与启动相应基因的转录,所述基因末端(GE)信号存在于每个基因的下游末端并参与指导polyA尾的合成,然后释放mRNA。

[0008] RSV疫苗的开发自1960年代以来一直在进行中,但由于许多因素而变得复杂。例如,已经显示用灭活的RSV免疫未经历RSV的婴儿在随后的天然RSV感染中引发增强的疾病,并且在实验动物中的研究表明疾病增强也与纯化的RSV亚单位疫苗相关。

[0009] 免疫保护的另一个障碍是RSV在呼吸道腔的表面细胞中复制并引起疾病,其中免疫保护具有降低的有效性。因此,RSV感染的免疫控制是低效的并且通常是不完全的,并且RSV疫苗尽可能具有免疫原性是重要的。RSV疫苗的另一个障碍是保护性免疫应答的大小与病毒复制(和抗原产生)的程度大致成比例。因此,制备活疫苗所必需的RSV的减弱通常伴随着复制和抗原合成的减少,以及免疫原性的伴随性降低,因此鉴定耐受性良好以及具有令人满意的免疫原性的复制水平是有益的。

[0010] 另一个障碍是RSV在细胞培养中仅生长到适度的滴度,并且通常存在于难以纯化的长丝中。RSV在处理过程中很容易失去感染性。另一个障碍是难以鉴别和开发减毒突变。适当的突变必须在体内是减毒的,但对体外复制应该是最低限制的,因为这对于有效的疫

苗生产是优选的。另一个障碍是RNA病毒特有的遗传不稳定性，其中减毒突变可以转变为野生型(wt)分配或赋予非减毒表型的替代分配。对于点突变，不稳定性和去减毒特别成问题。

[0011] 综合考虑这些因素，需要在体外有效复制，具有最大免疫原性，令人满意地减毒并且难以去减毒的活减毒RSV株。

[0012] 概述

[0013] 本文公开了在产生表现出一系列减毒表型的人RSV的重组毒株中单独或组合(可包括其他已知突变)的有用的突变。突变干扰编码病毒M2-2蛋白的开放阅读框(ORF)的表达。还公开了RSV的重组株，其含有这样的突变，单独或与其他基因座处的一个或多个另外的突变组合，其可以减少或替代地增加减毒表型的量级。因此，本文公开了新型活减毒RSV株，其具有适合用作RSV疫苗的一系列减毒表型。在一些实例中，所公开的重组RSV的实施方案显示为感染性的、减毒的和自我复制的，并且在人受试者中引起令人惊讶的高滴度的中和抗体。

[0014] 在一些实施方案中，提供重组RSV，其通过对病毒基因组的一种或多种修饰减毒，如干扰编码病毒M2-2蛋白的开放阅读框(ORF)的表达的修饰。在一些实施方案中，重组RSV的基因组包含一种或多种修饰，其中所述一种或多种修饰包括在M2-2ORF中对应SEQ ID NO:1的位置8189-8429的241个核苷酸的缺失的缺失组合在对应SEQ ID NO:1的位置T8161、T8167和T8179的核苷酸突变，如T变成C的取代(“ΔM2-2”)。所述核苷酸突变破坏这些位置处的翻译起始密码子。在一些实施方案中，重组RSV的基因组包含一种或多种修饰，其中所述一种或多种修饰包括在M2-2ORF中对应SEQ ID NO:1的位置8203-8436的234个核苷酸的缺失的缺失组合在对应SEQ ID NO:1的位置T8198和C8200的核苷酸突变T8198A和C8200G(“ΔM2-2-AclI”)。在一些实施方案中，重组RSV的基因组包含一种或多种修饰，其中所述一种或多种修饰包括在M2-2ORF中对应SEQ ID NO:1的位置8203-8436的234个核苷酸的缺失的缺失组合在对应SEQ ID NO:1的位置T8198和C8199的核苷酸突变T8198A和C8199G(“ΔM2-2-HindIII”)，其中所述重组RSV基因组是通过所述一种或多种修饰减毒的D46基因组

[0015] 除了干扰编码病毒M2-2蛋白的开放阅读框(ORF)的表达的修饰之外，重组RSV的基因组可包括其他修饰以增加或减少病毒减毒，或重组病毒的其他性质。在一些实施方案中，所述一种或多种对重组RSV的基因组的修饰可进一步包括对应SEQ ID NO:1的位置4499-4610的112个核苷酸的缺失组合在对应SEQ ID NO:1的位置C4489、C4492、A4495、A4497和G4498的核苷酸突变C4489T、C4492T、A4495T、A4497G和G4498A(“6120”)。例如，在一些实施方案中，重组RSV通过对一种或多种基因组修饰减毒，其中所述一种或多种基因组修饰包括在M2-2ORF中对应SEQ ID NO:1的位置8203-8436的234个核苷酸的缺失组合在对应SEQ ID NO:1的位置T8198和C8199的核苷酸突变T8198A和C8199G(“ΔM2-2-HindIII”)，和对应SEQ ID NO:1的位置4499-4610的112个核苷酸的缺失组合在对应SEQ ID NO:1的位置C4489T、C4492T、A4495T、A4497G和G4498A的核苷酸突变(“6120”)。

[0016] 在一些实施方案中，对重组RSV基因组的一种或多种修饰进一步包括编码RSV的N蛋白中的V267I、F蛋白中的E218A和T523I和L蛋白中的C319Y和H1690Y的氨基酸取代的核苷酸突变(“cp”)。在一些实施方案中，对重组RSV基因组的一种或多种修饰进一步包括在RSV的L蛋白中引入Y1321K取代的核苷酸突变，且其中所述L蛋白包括S1313残基，其中编码Y1321K取代和S1313残基的密码子分别是AAA和TCA密码子(“1030s”)。在一些实施方案中，

对重组RSV基因组的一种或多种修饰进一步包括编码RSV的NS2蛋白中的氨基酸取代K51R的核苷酸突变(“NS2”)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括编码RSV的N蛋白中的氨基酸取代T24A的核苷酸突变(“N”)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括编码RSV的NS2蛋白中的K51R和N蛋白中的T24A的氨基酸取代的核苷酸突变(“NS2/N”)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括在SH ORF中对应SEQ ID NO:1的位置4198-4616的419个核苷酸的缺失的缺失(“ΔSH”)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括将编码RSV的G蛋白的核苷酸序列替换为编码来自临床分离株A/Maryland/001/11的G蛋白的相应密码子优化的核苷酸序列(如SEQ ID NO:8,G001BB)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为SEQ ID NO:9所述的相应密码子优化的核苷酸序列(FBB)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为编码来自临床分离物A/Maryland/001/11的F蛋白的SEQ ID NO:10所述的相应核苷酸序列(F001)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括将编码RSV的F蛋白的核苷酸序列替换为编码来自临床分离株A/Maryland/001/11的F蛋白的相应密码子优化的核苷酸序列(如SEQ ID NO:11,F001BB)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括在RSV的F蛋白中编码氨基酸取代K66E和Q101P的核苷酸突变(“HEK”)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括编码RSV的F蛋白中的氨基酸取代E218A和T523I的核苷酸突变(F cp取代)。在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括逆转编码RSV基因组中G和F蛋白的基因的顺序。

[0017] 在一些实施方案中,对重组RSV基因组的一种或多种修饰进一步包括选自以下任一项的突变的组合或由其组成:ΔM2-2、cp/ΔM2-2、cp/ΔM2-2/HEK、ΔM2-2/1030s、NS2/N/ΔM2-2、NS2/ΔM2-2、N/ΔM2-2、ΔSH/ΔM2-2、cp/ΔSH/ΔM2-2、6120/ΔM2-2、6120/cp/ΔM2-2、6120/ΔM2-2/1030s、6120/NS2/N/ΔM2-2、6120/G001BB/FBB/ΔM2-2、6120/FBB/G001BB/ΔM2-2、6120/G001BB/F/ΔM2-2、6120/G/FBB/ΔM2-2、6120/G/FBBHEK/ΔM2-2、6120/G/FBBcpHEK/ΔM2-2、6120/FBB/G/ΔM2-2、6120/G001BB/F001BB/ΔM2-2、6120/NS2/ΔM2-2或6120/N/ΔM2-2;或ΔM2-2-AclI、cp/ΔM2-2-AclI、cp/ΔM2-2-AclI/HEK、ΔM2-2-AclI/1030s、NS2/N/ΔM2-2-AclI、NS2/ΔM2-2-AclI、N/ΔM2-2-AclI、ΔSH/ΔM2-2-AclI、cp/ΔSH/ΔM2-2-AclI、6120/ΔM2-2-AclI、6120/cp/ΔM2-2-AclI、6120/ΔM2-2-AclI/1030s、6120/NS2/N/ΔM2-2-AclI、6120/G001BB/FBB/ΔM2-2-AclI、6120/FBB/G001BB/ΔM2-2-AclI、6120/G001BB/F/ΔM2-2-AclI、6120/G/FBB/ΔM2-2-AclI、6120/G/FBBHEK/ΔM2-2-AclI、6120/G/FBBcpHEK/ΔM2-2-AclI、6120/FBB/G/ΔM2-2-AclI、6120/G001BB/F001BB/ΔM2-2-AclI、6120/NS2/ΔM2-2-AclI或6120/N/ΔM2-2-AclI;or ΔM2-2-HindIII;cp/ΔM2-2-HindIII、cp/ΔM2-2-HindIII/HEK、ΔM2-2-HindIII/1030s、NS2/N/ΔM2-2-HindIII、NS2/ΔM2-2-HindIII、N/ΔM2-2-HindIII、ΔSH/ΔM2-2-HindIII、cp/ΔSH/ΔM2-2-HindIII、6120/ΔM2-2-HindIII、6120/cp/ΔM2-2-HindIII、6120/ΔM2-2-HindIII/1030s、6120/NS2/N/ΔM2-2-HindIII、6120/G001BB/FBB/ΔM2-2-HindIII、6120/FBB/G001BB/ΔM2-2-HindIII、6120/G001BB/F/ΔM2-2-HindIII、6120/G/FBB/ΔM2-2-HindIII、6120/G/FBBHEK/ΔM2-2-HindIII、6120/G/FBBcpHEK/ΔM2-2-HindIII、6120/FBB/G/ΔM2-

2-HindIII、6120/G001BB/F001BB/ΔM2-2-HindIII、6120/NS2/ΔM2-2-HindIII或6120/N/ΔM2-2-HindIII。

[0018] 在一些实施方案中，重组RSV的基因组包括如上文讨论的一种或多种突变和对应于与SEQ ID NO:1(D46序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组重组RSV的基因组是以如上文讨论的一种或多种突变修饰的D46基因组。在一些实施方案中，重组RSV的基因组包括6120和ΔM2-2突变和对应于与SEQ ID NO:5(LID/ΔM2-2序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括cp和ΔM2-2突变，和对应于与SEQ ID NO:1(D46序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括cp和ΔM2-2突变，和对应于与SEQ ID NO:15(D46/cp/ΔM2-2序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括6120、ΔM2-2和1030s突变，和对应于与SEQ ID NO:16(LID/ΔM2-2/1030s序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括6120、cp和ΔM2-2突变，和对应于与SEQ ID NO:17(LID/cp/ΔM2-2序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括NS2、N、ΔM2-2-HindIII突变，和对应于与SEQ ID NO:4(D46/ΔM2-2-HindIII序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括NS2、N、ΔM2-2-HindIII突变，和对应于与SEQ ID NO:18(D46/NS2/N/ΔM2-2-HindIII序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括NS2、N、ΔM2-2-AclI突变，和对应于与SEQ ID NO:3(D46/ΔM2-2-AclII序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。在一些实施方案中，重组RSV的基因组包括NS2、N和ΔM2-2-AclI突变，具有相对SEQ ID NO:1位置的下述核苷酸突变:404C、779G、C1099缺失、1139A、1140G、1182G、1210G、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T和13634A;和对应于与SEQ ID NO:19(276序列)至少90％(如至少95％或至少99％)相同的正义序列的核苷酸序列。

[0019] 在一些实施方案中，重组RSV的基因组是D46/cp/ΔM2-2基因组、LID/ΔM2-2/1030s基因组、LID/cp/ΔM2-2基因组、D46/NS2/N/ΔM2-2-HindIII基因组、LID/ΔM2-2基因组或276基因组。在一些实施方案中，重组RSV的基因组包括对应于下述任一项所述的正义序列的核苷酸序列或由其组成:SEQ ID NO:2、SEQ ID NO:3、SEQ ID NO:4、SEQ ID NO:5、SEQ ID NO:6、SEQ ID NO:7、SEQ ID NO:15、SEQ ID NO:16、SEQ ID NO:17、SEQ ID NO:18或SEQ ID NO:19。

[0020] 在一些实施方案中，重组RSV的基因组包括对应于如SEQ ID NO:3所述的正义序列的核苷酸序列，其进一步通过引入下述相对SEQ ID NO:1的核苷酸突变修饰:404C、779G、1099T、1139A、1140G、1182G、1210G、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T和13634A。在一些实施方案中，重组RSV的基因组包括对应于如SEQID NO:3所述的正义序列的核苷酸序列，其进一步通过引入下述相对SEQ ID NO:1的核苷酸突变修饰:404C、779G、C1099缺失、1139A、1140G、1182G、1210G、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T和13634A。在一些实施方案中，重

组RSV的基因组包括选自下组的序列:SEQ ID NO:2、SEQ ID NO:3和SEQ ID NO:4,其进一步通过引入具有下述一种或多种相对SEQ ID NO:1位置的核苷酸取代修饰:404C、779G、1099T、1139A、1140G、1182G、1210G、1938A、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T、13634A、13901T。

[0021] 本文公开的重组RSV的实施方案可以是亚型A RSV或亚型B RSV。本文公开的重组RSV的实施方案是感染性、减毒和自我复制的。

[0022] 本文还公开了与本文公开的病毒的表达相关的方法和组合物。例如,公开了包括编码编码所述病毒的基因组或反基因组的核酸序列的分离的多核苷酸分子。

[0023] 还提供了包含所述重组RSV的药物组合物。所述组合物可进一步包含佐剂。还公开了通过向受试者施用免疫原性有效量的公开的重组RSV在受试者中引发免疫应答的方法。在一些实施方案中,受试者是人受试者,例如1至6月龄,或1至12月龄,或1至18月龄或更大的人受试者.

[0024] 通过参考附图进行的若干实施方案的以下详细描述,本公开的前述和其他特征和优点将变得更加明显。

[0025] 附图简述

[0026] 图1A和1B RSV基因组中的“ΔM2-2”突变通过引入241-nt缺失并消除M2-2蛋白的三个潜在翻译起始密码子来沉默RSV骨架中的M2-2ORF。序列编号是根据wt人RSV株A2的完整序列,其由GenBank登录号M74568表示,其通过引用并入本文。(图1A)RSV基因组的组织和重叠的M2-1和M2-2ORF。显示了M2-2ORF的三个潜在的ATG翻译起始密码子。(图1B)ΔM2-2突变的细节。上部核苷酸序列是生物wt RSV(M74568)的核苷酸序列,并且显示对应于SEQ ID NO:1的8150-8204和8247-8440的核苷酸。M74568和SEQ ID NO:1之间的核苷酸编号偏离一个核苷酸,因为与M74568相比,SEQ ID NO:1的1099位的单核苷酸插入。紧接下面的氨基酸序列是M2-1蛋白的C末端(SEQ ID NO:12)。下一个氨基酸序列是M2-2蛋白的N-末端残基(SEQ ID NO:13)。M2-2ORF的三个潜在的ATG起始密码子用框和粗体表示。第二核苷酸序列(对于ΔM2-2突变)显示使M2-2ORF沉默的突变(显示SEQ ID NO:1的核苷酸8150-8188和8430-8440,氨基酸序列SEQ ID NO:13直接显示在下面)。对于ΔM2-2突变,三个潜在的翻译ATG起始位点中的每一个都变为ACG,并且缺失M74568核苷酸8188至8428,去除241个核苷酸。TER,翻译终止密码子。

[0027] 图2.描述了使用D46骨架并包含ΔM2-2突变的减毒重组RSV的两个实例的基因图谱。这些是D46/ΔM2-2(包含ΔM2-2突变)和LID/ΔM2-2(包含ΔM2-2突变和“6120”突变,参见图3)病毒。这两种构建体的反基因组cDNA序列分别用SEQ ID NO:2和SEQ ID NO:5表示。

[0028] 图3A和3B.RSV基因组中的“6120”突变包含SH基因的下游非翻译区中的112个核苷酸缺失。序列编号是根据wt人RSV株A2的完整序列,其由GenBank登录号M74568表示。RSV基因组图(图3A)和含有“6120”突变的SH基因(图3B)的下游末端,其存在于LID/ΔM2-2中。在本公开中,病毒名称中“6120”的使用表明存在6120突变。(图3A)RSV基因组图。箭头表示SH基因下游非翻译区中6120突变的位置。(图3B)6120突变的细节。上部核苷酸序列是生物wt RSV(M74568)的序列,并且显示SEQ ID NO:1的核苷酸4481-4498和4611-4632,其对应于SH基因的下游末端。显示了SH ORF的最后五个密码子,提供了相应的氨基酸序列(ARVNT,SEQ ID NO:14),然后是翻译终止密码子(TER)。其后右侧是SH基因的下游非翻译区(SEQ ID NO:

1的核苷酸4611-4632)，SH基因末端信号加下划线。三个点代表在6120突变中缺失的下游非翻译区(M74568核苷酸4498-4609)的112个核苷酸。较低的核苷酸序列(显示SEQ ID NO:5的核苷酸4481-4520，提供了相应的氨基酸序列(ARVNT，SEQ ID NO:14))描述了6120突变，其包括112个核苷酸缺失以及在下游三个密码子和SH ORF的终止密码子中的5个沉默点突变(粗体)。天然存在的XhoI和PacI限制性位点用斜体表示。

[0029] 图4.RSV D46/ΔM2-2衍生物的三个实例的基因组的示意图，其各包含一个或多个额外的减毒突变。描绘了ΔM2-2突变。其他减毒突变包括一组“cp”突变(N，F和L蛋白中的五个氨基酸取代:N(V267I)，F(E218A和T523I)和L(C319Y和H1690Y))，以及L蛋白中稳定的1030突变(“1030s”)突变，其包括通过引入L氨基酸1321的AAA密码子产生的Y1321K取代，以及L位置1313的丝氨酸密码子的稳定形式(SEQ ID NO:1的nt 12435-12437;AGC变为TCA)(1321K(AAA)+S1313(TCA);Luongo,et al.2012.J Virol 86:10792-10804)。进一步的突变是F蛋白中的HEK变化(K66E和Q101P)(Connors,et al.1995.Virology 208:478-484;Whitehead,et al.1998.JVirol 72:4467-4471)。

[0030] 图5.RSV LID/ΔM2-2衍生物的四个实例的基因组的示意图，其各包含一个或多个额外的减毒突变。“LID”骨架是基于D46的基因组，其含有“6120”突变。指示了ΔM2-2突变和6120突变。其他减毒突变包括一组“cp”突变(N、F和L蛋白中的五个氨基酸取代:N(V267I)、F(E218A和T523I)和L(C319Y和H1690Y))，SH基因的缺失(参见图6)和L蛋白中的“1030s”突变。注意，已缺失整个SH基因的病毒(RSVΔSH/ΔM2-2和RSV cp/ΔSH/ΔM2-2)不称为“LID”，因为SH缺失除去了6120突变。

[0031] 图6.“ΔSH”突变的细节，其为沉默SH基因的419个核苷酸缺失。序列编号是根据wt人RSV毒株A2的完整序列，其由GenBank登录号M74568表示。在上面的序列中(显示SEQ ID NO:1的核苷酸4191-4229和4617-4637)，从左到右的特征包括:M基因末端信号(下划线)、M/SH基因间序列(IGS)、SH基因起始信号(下划线)、表示SH基因的主体的三个点(M74568核苷酸4229-4615，未显示)、SH基因末端信号(下划线)和部分SH/G IGS。底部序列(SEQ ID NO:1的核苷酸4191-4197和4617-4637)说明产生ΔSH突变的419-核苷酸缺失。注意，虽然这在操作上被称为SH基因的缺失，但实际上缺失从M基因末端信号的紧邻上游跨越到SH基因末端信号的紧邻上游。

[0032] 图7.在BALB/c小鼠中复制示例性重组RSV。显示了RSV D46(重组wt亲本)、RSV LID/ΔM2-2、RSVΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s和RSV cp/ΔSH/ΔM2-2在BALB/c小鼠的呼吸道中的复制结果，其中通过RT-qPCR评估在鼻甲和肺中的复制。通过鼻内(IN)途径用0.1ml中的5.8$\log_{10}$PFU的所示病毒接种组中的10只小鼠(或对于RSV D46为12只)。在第4天和第5天(D4，D5)处死每种病毒的5只小鼠(或对于RSV D46为6只)，取出鼻甲和肺，均质化，并通过对RSV M基因特异的RT-qPCR进行评估，拷贝数相对于平行评估的克隆的M cDNA确定。LoD:检测限。

[0033] 图8A和8B.在非洲绿猴(AGM)的呼吸道中复制示例性RSV重组病毒。显示了通过RT-qPCR评估具有脱落的AGM呼吸道中RSV LID/ΔM2-2、RSVΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s和RSV cp/ΔSH/ΔM2-2的复制数据。以(每位点)1.0ml中的6.0$\log_{10}$PFU的所示病毒通过组合的IN和气管内(IT)途径接种组中的4个AGM。通过对RSV M基因特异的RT-qPCR评估来自所示天数的鼻咽(NP)拭子和气管灌洗物，基于平行中评估的克隆M cDNA确定拷贝数。绘

制的结果来自实施例2、表1和2中描述的测定。

[0034] 图9A和9B.血清阴性婴儿和儿童中示例性重组RSV的峰值滴度。显示了单次IN接种后血清阴性婴儿和儿童(6-24月龄)的鼻洗液中RSV MEDI/ΔM2-2和RSV rA2cp248/404/1030ΔSH(图9A)或RSV LID/ΔM2-2(图9B)的峰值滴度。RSV MEDI/ΔM2-2和rA2cp248/404/1030ΔSH的结果来自Karron,et al.2015.Science Transl Med 2015 7(312):312ra175。通过鼻洗样本的噬斑滴定测定病毒滴度:来自RSV MEDI/ΔM2-2和RSV rA2cp248/404/1030ΔSH研究的样品并排测定,而来自RSV LID/ΔM2-2的样本分别测定。符号表示个别受试者的峰值。显示了平均峰值滴度。疫苗接种者各接受5.0$\log_{10}$PFU(RSV MEDI/ΔM2-2,RSV LID/ΔM2-2)或5.3$\log_{10}$PFU(RSV rA2cp248/404/1030ΔSH)疫苗病毒的单次IN剂量。rA2cp248/404/1030ΔSH候选疫苗的原始报告是Karron,et al.2005.J Infect Dis 191:1093-1104。

[0035] 图10A和10B.对RSV基因组的“ΔM2-2-AclI”和“ΔM2-2-HindIII”突变。ΔM2-2-AclI突变通过定点诱变使M2-2ORF沉默以缺失234个核苷酸并引入两个点突变,产生AclI限制性位点和翻译终止位点(TER)。ΔM2-2-HindIII突变通过定点诱变使M2-2ORF沉默以缺失234个核苷酸并引入两个点突变,产生HindIII限制性位点和翻译终止位点(TER)。序列编号是根据wt人RSV毒株A2的完整序列,其由GenBank登录号M74568表示。图10A显示了RSV基因组和重叠的M2-1和M2-2ORF的组织。显示了M2-2 ORF的三个潜在的ATG翻译起始密码子,但在ΔM2-2-AclI和ΔM2-2-HindIII突变中未被修饰。图10B显示ΔM2-2-AclI和ΔM2-2-HindIII突变的细节。上部核苷酸序列(SEQ ID NO:1的核苷酸8150-8204和8427-8440)是生物wtRSV(M74568)的核苷酸序列。紧接下面的氨基酸序列是M2-1蛋白(SEQ IDNO:12)的C末端。下一个氨基酸序列是M2-2蛋白(SEQ ID NO:13)的N-末端部分。M2-2ORF的三个潜在的ATG起始密码子用框和粗体表示。第二核苷酸序列(SEQ ID NO:3的核苷酸8150-8202)显示ΔM2-2-AclI突变的序列,其由核苷酸8202-8435的缺失和点突变T8197A和C8199G的引入产生,以在M2-2ORF中生成AclI位点以及密码子13处的TAA终止密码子。氨基酸序列12和13显示在ΔM2-2-AclI序列下。第三核苷酸序列(SEQ ID NO:4的核苷酸8150-8202)显示ΔM2-2-HindIII突变的序列,其由核苷酸8202-8435的缺失和点突变T8197A和C8198G的引入产生,以在M2-2ORF中生成HindIII位点以及密码子13处的TAA终止密码子。如图所示,ΔM2-2-AclI和ΔM2-2-HindIII中的突变的M2-2ORF具有编码代表M2-2蛋白的N-末端的12-氨基酸肽的潜力。氨基酸序列12和13显示在ΔM2-2-HindIII序列下。

[0036] 图11.携带ΔM2-2-AclI突变的RSV D46和LID基因组的示意图,称为D46/ΔM2-2-AclI and LID/ΔM2-2-AclI。这两种构建体的反基因组cDNA序列分别用SEQ ID NO:3和SEQ ID NO:6表示。

[0037] 图12A-12C.其中引入了K51R(NS2基因)和T24A(N基因)突变的ΔM2-2病毒的实例的基因组的示意图。在病毒名称中,K51R和T24A分别缩写为“NS2”和“N”。图12A显示将K51R和T24A突变一起引入D46/ΔM2-2-AclI骨架和LID/ΔM2-2-AclI骨架。图12B和12C示出了单独或一起将K51R和T24A突变引入D46/ΔM2-2骨架(图12B),或单独或一起引入LID/ΔM2-2骨架(图12C)。

[0038] 图13.具有“ΔM2-2-HindIII”突变的RSV D46和LID衍生物的实例的基因组的示意图,以及携带ΔM2-2-HindIII基因组并组合K51R和T24A突变的衍生物。单独将ΔM2-2-HindIII突变引入D46或LID骨架导致基因组D46/ΔM2-2-HindIII和LID/ΔM2-2-HindIII

(自顶部的第一和第三基因组)。将ΔM2-2-HindIII突变引入D46或LID骨架并组合K51R和T24A突变导致基因组D46/NS2/N/ΔM2-2-HindIII和LID/NS2/N/ΔM2-2-HindIII(自顶部的第二和第四基因组)。D46/ΔM2-2-HindIII和RSV LID/ΔM2-2-HindIII构建体的序列分别由SEQ ID NO:4和SEQ ID NO:7表示。

[0039] 图14A和14B.RSV LID/ΔM2-2衍生物实例(即含有图1中所示的ΔM2-2突变和图3中所示的6120突变)的基因组的示意图,其包含对F和G基因的额外修饰。对于这些构建体,使用识别号“6120”代替“LID”来指代6120突变。G001和F001分别指称为RSV A/Maryland/001/11的亚组A株(非A2)的临床分离株的G和F基因。所有其他基因来自株A2。“BB”指密码子优化的序列。HEK是指F蛋白中的两个氨基酸取代K66E和Q101P。在这种情况下,“FBBcpHEK”指密码子优化的F序列,其进一步包括HEK取代,以及落入F蛋白内的“cp”取代,即E218A和T523I。

[0040] 图15.图14A和14B中所示的构建体在Vero细胞中的病毒产量。P1滴度是转染后第一次传代的产量(盲测完成,即没有定量输入感染复数,MOI)。P2滴度是第二次传代的产量,以0.01PFU/细胞的输入MOI完成;注意,一种病毒由P3代表,MOI 0.001下第三代的产量。Wt LID是含有6120突变的D46。

[0041] 图16.说明RSV D46/276/ΔM2-2-AclI的基因组的示意图。

[0042] 序列表

[0043] 所附序列表中列出的核酸和氨基酸序列使用核苷酸碱基的标准字母缩写和氨基酸的三字母代码显示,如37C.F.R.1.822.中所定义。序列表作为ASCII文本文件以名为“Sequence.txt”(～240kb)的文件的形式提交,该文件于2016年12月8日创建,并且其通过引用并入本文。在随附的序列表中:

[0044] SEQ ID NO:1是重组RSV株D46的反基因组cDNA序列。

[0045] SEQ ID NO:2是重组RSV株D46/ΔM2-2的反基因组cDNA序列。

[0046] SEQ ID NO:3是重组RSV株D46/ΔM2-2-AclI的反基因组cDNA序列。

[0047] SEQ ID NO:4是重组RSV株D46/ΔM2-2-HindIII的反基因组cDNA序列。

[0048] SEQ ID NO:5是重组RSV株LID/ΔM2-2的反基因组cDNA序列。

[0049] SEQ ID NO:6是重组RSV株LID/ΔM2-2-AclI的反基因组cDNA序列。

[0050] SEQ ID NO:7是重组RSV株LID/ΔM2-2-HindIII的反基因组cDNA序列。

[0051] SEQ ID NO:8是编码G001BB的示例性多核苷酸序列。

[0052] SEQ ID NO:9是编码FBB的示例性多核苷酸序列。

[0053] SEQ ID NO:10是编码F001的示例性多核苷酸序列。

[0054] SEQ ID NO:11是编码F001BB的示例性多核苷酸序列。

[0055] SEQ ID NO:12是M2-1蛋白的C末端氨基酸序列(SDTNDHAKNNDTT)。

[0056] SEQ ID NO:13是M2-2蛋白的N-末端氨基酸序列(MTMPKIMILPDKYPC)。

[0057] SEQ ID NO:14是SH蛋白的C末端氨基酸序列(ARVNT)。

[0058] SEQ ID NO:15是重组RSV株D46/cp/ΔM2-2的反基因组cDNA序列。

[0059] SEQ ID NO:16是重组RSV株LID/ΔM2-2/1030s的反基因组cDNA序列。

[0060] SEQ ID NO:17是重组RSV株LID/cp/ΔM2-2的反基因组cDNA序列。

[0061] SEQ ID NO:18是重组RSV株D46/NS2/N/ΔM2-2-HindIII的反基因组cDNA序列。

[0062] SEQ ID NO:19是重组RSV毒株“276”的反基因组cDNA序列。

[0063] SEQ ID NOs:20和21是基因起始转录信号的核苷酸序列(分别为GGGGCAAATA和GGGGCAAACA)。

[0064] 发明详述

[0065] 本文提供了适合用作人类减毒活疫苗的重组RSV毒株。通过引入阻断M2-2蛋白表达并赋予减毒的突变来产生RSV株。进一步提供了重组RSV株,其中阻断M2-2蛋白表达的突变与一个或多个其他基因座的一个或多个额外的工程化突变组合存在,其增加或减少减毒幅度,提供具有分级减毒程度的候选疫苗。

[0066] 减少或消除M2-2ORF表达的突变导致病毒基因的表达上调,包括编码保护性抗原的那些(Bermingham and Collins.1999.Proc Natl Acad Sci USA 96:11259-11264),并具有赋予增强的免疫原性的潜力。然而,先前未证实增加的免疫原性,并且在包括黑猩猩的实验动物中不明显(Teng,et al.2000.J Virol 74:9317-9321)。对含有本文所述M2-2突变的本文公开株的临床评价表明,这些毒株表现出增强的免疫原性。对代表主要疫苗靶标群体的血清阴性婴儿和儿童的研究表明,本文公开的株是减毒的并且通常耐受良好,并且诱导显著高于先前RSV疫苗候选(rA2cp248/404/1030ΔSH)的RSV中和血清抗体实质滴度,所述先前RSV疫苗候选具有不同的减毒基础(即几种病毒基因中的一系列点突变,包括聚合酶,代表一种更典型的活疫苗候选物),并在类似的受试者群体中评估(Karron,et al.2005.J Infect Dis 191:1093-1104)。

[0067] 因此,本公开内容提供了新的,改进的具有新型M2-2缺失突变的减毒RSV毒株,其在人体中具有增强的免疫原性。使用消除大部分病毒ORF的大缺失提供了遗传稳定性。此外,本公开内容提供了具有与修饰表型的其他突变组合的M2-2缺失突变的新型减毒RSV株。这提供了具有分级减毒表型的病毒株。

[0068] 本发明的重组RSV株包含野生型RSV基因组或反基因组,其含有如下详述的进一步修饰或突变。野生型RSV病毒基因组或反基因组编码以下11种蛋白:RNA结合核蛋白(N)、磷蛋白(P)、大聚合酶蛋白(L)、附着糖蛋白(G)、融合蛋白(F)、小疏水性(SH)表面糖蛋白、内部基质蛋白(M)、两种非结构蛋白NS1和NS2以及M2-1和M2-2蛋白。RSV基因顺序为:3’-NS1-NS2-N-P-M-SH-G-F-M2-L。这些蛋白质的完整氨基酸序列是本领域已知的。

[0069] 鉴于存在多种RSV株(例如,RSV A2、RSV B1、RSV Long),本领域的技术人员将理解,某些RSV株可具有改变给定残基位置的核苷酸或氨基酸插入或缺失。例如,如果另一种RSV株的蛋白质与株A2相比,在蛋白质的上游末端具有两个额外的氨基酸,这将导致相对于株A2的下游残基的氨基酸编号增加2。然而,因为这些毒株具有很大程度的序列同一性,所以本领域技术人员能够通过简单地将A2参考株的核苷酸或氨基酸序列与感兴趣的株的核苷酸或氨基酸序列比对来确定相应序列的位置。因此,应当理解,尽管在本公开内容的上下文中具体列举,但在发生序列迁移时或由于病毒株之间的序列变异时,本文所述的氨基酸和核苷酸位置可以对应于其他位置。在两种或多种相关病毒之间的蛋白质,或蛋白质区段,或基因,或基因组或基因组区段的比较中,“相应的”氨基酸或核苷酸残基是被认为是在不同物种中在功能上完全或近似等同的氨基酸或核苷酸残基。

[0070] 除非上下文另有说明,否则本公开中使用的编号以野生型RSV A2株的序列(GenBank登录号M74568)为基础,并且所述的病毒基因组序列是正义的。

[0071] 在本发明的一些实施方案中，重组RSV株衍生自称为D46的株A2的重组形式。D46的完整序列显示在美国专利6,790,449中，并且在本文中提供为SEQ ID NO:1。(在一些情况和出版物中，亲本病毒和序列称为D53而不是D46，这是一种书本保持的差异，指的是用于繁殖反基因组cDNA的细菌菌株，且没有其他已知的显著性或效果。就本发明而言，D46和D53是可互换的)。SEQ ID NO:1(D46的核苷酸序列)在25个核苷酸位置不同于RSV A2株M74568的序列，其在位置1099包括1-nt的插入。因此，当核苷酸位于超过核苷酸1099某一位置时，相对于SEQ ID NO:1的序列编号与相对于M74568的编号区别为增加1个核苷酸。

[0072] 在一些实施方案中，RSV基因组或反基因组通过M2-2ORF中的缺失进行修饰。RSV M2-2蛋白由M2mRNA中的第二个下游ORF编码，其与5'近端的上游M2-1ORF略微重叠(图1A)。有三种潜在的翻译起始密码子可以产生株A2长度为90、88和84个氨基酸的产物(图1B中的方框)。本文描述的M2-2突变包括缺失涉及大部分M2-2ORF的大量核苷酸(通常各多于200个核苷酸)，因此大部分或完全消除M2-2蛋白的表达。因此，M2-2突变对于可能导致减毒损失的补偿或逆转是困难的。这种遗传稳定性在临床研究中得到证实。大多数先前的RSV候选疫苗涉及减毒点突变，其易于逆转或补偿，导致去减毒(例如，Karron,et al.2005.J Infect Dis 191:1093-1104;Malkin,et al.2013.PLoS One 8:e77104;Karron,Buchholz,Collins.2013.Curr Top Microbiol Immunol 372:259-284)。去减毒有可能增加疫苗接种者的病毒复制，这可能导致反应原性，并且还有可能使减毒不足的衍生物传播到易感接触者。因此，本文所述的M2-2突变消除了RSV疫苗开发的主要问题。

[0073] 在一些实施方案中，M2-2突变包含位于8188-8428位(SEQ ID NO:1的8189-8429)的241个核苷酸的缺失和突变T8160C、T8166C和T8178C(SEQ ID NO:1的T8161C、T8167C和T8179C)，其消除三个潜在的起始密码子。该突变在图1B中解释，并且在本文中称为“ΔM2-2”突变。

[0074] 在一些实施方案中，M2-2突变包含位于8202-8435位(SEQ ID NO:1的8203-8436)的234个核苷酸的缺失，并且组合8197A和8199G(SEQ ID NO:1的8198A和8200G)的存在，其对应于AclI限制酶位点的存在。该突变在图10中解释，并且在本文中称为“ΔM2-2-AclI”突变。

[0075] 在一些实施方案中，M2-2缺失包含位于8202-8435位(SEQ ID NO:1的8203-8436)的234个核苷酸突变，并且组合8197A和8198G(SEQ ID NO:1的8198A和8199G)的存在，其对应于HindIII限制酶位点的存在。该突变在图10中解释，并在本文中称为“ΔM2-2-HindIII”突变。在一些实施方案中，用于构建所述株的RSV毒株可以是D46(SEQ ID NO:1)。在这种情况下，得到的重组株称为D46/ΔM2-2-HindIII。

[0076] 本公开中病毒名称中存在的术语“ΔM2-2”表示该病毒中存在图1中所示的ΔM2-2突变，除了“MEDI/ΔM2-2”的情况，其指在下面的实施例中描述的不同突变。其他突变由术语ΔM2-2-AclI或ΔM2-2-HindIII指定。

[0077] 可以与上文定义的M2-2突变之一组合进一步引入另外的突变以构建具有所需特征的另外的病毒株。例如，添加的突变可以指定不同的减毒量级，从而逐渐增加减毒。因此，候选疫苗株可以通过并入至少一种，优选两种或更多种不同的减毒突变进一步减毒，例如从一组已知的生物学衍生的突变RSV株中鉴定的突变。这里讨论了许多这样的突变作为实例。从该示例性组中可以产生大“列表”的减毒突变，其中每个突变可以与组内的任何其他

突变组合以校准减毒水平和其他预期的表型。可以在非RSV负链RNA病毒中鉴定另外的减毒突变，并通过将突变映射到受体RSV基因组或反基因组中的相应同源位点并将受体中的现有序列突变为突变体基因型(通过相同或保守的突变)而并入本发明的RSV突变体中。其他有用的突变可以通过使用重组小基因组系统和感染性病毒的突变分析凭经验确定，如本文引用的参考文献中所述。

[0078] 在一些实施方案中，所公开的重组RSV疫苗株可以使用称为反向遗传学的基于重组DNA的技术产生(Collins,et al.1995.Proc Natl Acad Sci USA 92:11563-11567)。该系统允许在限定的条件下从合格的细胞底物中完全从cDNA中重新回收感染性病毒。反向遗传学提供了通过cDNA中间体将预定突变引入RSV基因组的方法。在临床前研究中表征特异性减毒突变并组合以达到所需的减毒水平。从cDNA中衍生出疫苗病毒可以最大限度地降低外来因子污染的风险，并有助于保持传代史简短并有详细记录。一旦回收，工程化病毒株以与生物衍生病毒相同的方式繁殖。作为传代和扩增的结果，疫苗病毒不含有来自原始回收的重组DNA。

[0079] 包含本文讨论的各种组合的突变的重组病毒株仅用于示例性目的，并不意味着限制本发明的范围。此处未描述的其他减毒突变也可以与公开的M2-2突变(例如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变)组合使用。

[0080] 例如，在一些实施方案中，本发明的重组RSV株还包含非翻译序列的缺失。在一个实施方案中，这种缺失发生在SH基因的下游末端，导致本文称为“6120”突变的突变。“6120”突变如图3所示。它涉及缺失SH基因下游非翻译区的112个核苷酸，并在SH基因的最后三个密码子和终止密码子中引入五个翻译-沉默点突变(Bukreyev,et al.2001.J Virol 75:12128-12140)。重组病毒名称中存在术语“LID”或“6120”表示重组病毒含有6120突变。

[0081] 6120突变使细菌中的反基因组cDNA稳定，从而可以更容易地操作和制备。在wt RSV中，先前发现该突变使体外复制效率提高5倍(Bukreyev,et al.2001.J Virol 75:12128-12140)，而不认为其在体内增加复制效率。当评估RSV LID/ΔM2-2与6120突变相关的复制增加的可能性时，观察到生长效率的适度但不一致的增加。

[0082] 6120突变与血清阴性婴儿和儿童的复制增加有关。因此，6120突变提供了另一种改变减毒水平的方式。虽然本文结合ΔM2-2突变证明了该策略的使用，但为了相同的目的，它可以应用于其他减毒株。此外，SH基因的下游非翻译区域中的6120突变例示了序列的缺失，但原则上可涉及任何不包含关键顺式作用信号的相当的基因组序列(Collins and Karron.2013.Fields Virology 6th Edition,pp 1086-1123)。作为缺失候选的基因组区域包括但不限于其他基因、基因间区域和后随区域(trailer region)中的非翻译区域。

[0083] 在一些实施方案中，重组RSV毒株可包含“cp”突变。这种突变是指三种蛋白质(N(V267I)、F(E218A和T523I)和L(C319Y和H1690Y))中的一组五个氨基酸取代，它们在血清阴性黑猩猩中一起(凭其自身)赋予大约10倍的复制减少和疾病的减少(Whitehead,et al.1998.J Virol 72:4467-4471)。先前已显示cp突变与中度减毒表型相关(Whitehead,et al.1999.J Virol 72:4467-4471)。

[0084] 此外，先前对通过cpRSV的化学诱变衍生并选择用于温度敏感(ts)表型的6种生物病毒的分析产生了总共6种独立突变，每种突变均赋予ts减毒表型并且可以以多种组合使用。其中五个是L蛋白中的氨基酸取代，其基于病毒编号而不是序列位置命名:″955″

(N43I)、“530”(F521L)、“248”(Q831L)、“1009”(M1169V)和“1030”(Y1321N)(Juhasz,et al.1999.Vaccine 17:1416-1424;Collins,et al.1999.Adv Virus Res 54:423-451;Firestone,et al.1996.Virology 225:419-422;Whitehead,et al.1999.J Virol 73:871-877)。第六个突变(称为“404”)是M2基因的基因起始转录信号中的单核苷酸变化(GGGGCAAATA,SEQ ID NO:20至GGGGCAAACA,SEQ ID NO:21,mRNA有义)(Whitehead,et al.1998.Virology 247:232-239)。已经使用反向遗传来增加248和1030突变的遗传稳定性(Luongo,et al.2009.Vaccine 27:5667-5676;Luongo,et al.2012.J Virol 86:10792-10804)。此外,产生了一种新的减毒突变,其通过缺失L蛋白中密码子1313并将其与I1314L取代组合以赋予增加的遗传稳定性(Luongo,et al.2013.J Virol 87:1985-1996)。

[0085] 在一些实施方案中,重组株可包含F蛋白中的一种或多种变化,例如,“HEK”突变,其包含F蛋白中的两个氨基酸取代,即K66E和Q101P(描述于Connors,et al.1995.Virology 208:478-484;Whitehead,et al.1998.J Virol 72:4467-4471)。将HEK氨基酸分配(assignment)引入本公开的株A2F序列中导致F蛋白氨基酸序列与株A2的临床分离株的早期传代(人胚胎肾细胞传代7,HEK-7)相同(Connors,et al.1995.Virology 208:478-484;Whitehead,et al.1998.J Virol 72:4467-4471)。它导致F蛋白的融合性低得多,并且被认为代表了原始A2株临床分离株的表型(Liang et al.J Virol 2015 89:9499-9510)。HEK F蛋白还形成更稳定的三聚体(Liang et al.J Virol 2015 89:9499-9510)。这可以提供更真实和免疫原性形式的RSV F蛋白,可能富集高免疫原性的融合前构象(McLellan et al.Science 2013 340(6136):1113-7;Science 2013 342(6158):592-8.)。因此,可以引入突变,除了影响病毒复制的程度之外,还可以产生其他影响。

[0086] 在一些实施方案中,重组株可以包含L蛋白中的一种或多种变化,例如,稳定化的1030或“1030s”突变,其包含1321K(AAA)/1313S(TCA)(Luongo,et al.2012.J Virol 86:10792-10804)。

[0087] 在一些实施方案中,重组株可包含一种或多种RSV基因的缺失。单独和组合地缺失SH、NS1和NS2基因已经显示产生能够在细胞培养物中保留其复制能力但在体内以下述递增的顺序减毒的病毒:SH<NS2<NS1(Bukreyev,et al.1997.J Virol 71:8973-8982;Whitehead,et al.1999.J Virol 73:3438-3442;Teng,et al.2000.J Virol 74:9317-9321)。因此,SH、NS2或NS1基因或其部分ORF的缺失或其他突变可以与公开的M2-2突变(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变)组合。例如,在一些实施方案中,重组株可包含SH蛋白中的一种或多种变化,包括SH蛋白的消除(ablation)或去除(elimination)。在一些实施方案中,病毒株包含SH基因中的缺失。例如,在一些实施方案中,病毒株包含在4197-4615位(SEQ ID NO:1的4198-4616)的419个核苷酸缺失,在本文中表示为“ΔSH”突变。该缺失导致M基因末端,M/SH基因间区域的缺失和SH ORF的缺失,如图6所示。在一些实施方案中,重组株可包含NS1或NS2蛋白中的一种或多种变化,其可包括蛋白质的消除或去除。在一些实施方案中,突变可以是NS2蛋白中的氨基酸取代如K51R。在一些实施方案中,重组株可包含N蛋白中的一种或多种变化,例如,氨基酸取代如T24A。

[0088] 可以向具有公开的M2-2突变(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变)的RSV株引入各种特征,其以非减毒的其他方式改变病毒的特征。例如,可以进行编码蛋白质的ORF的密码子优化。主要保护性抗原F和G可导致抗原合成增加。F和/或G蛋白基因可以向

上游迁移(更靠近启动子)以增加表达。然而,本公开还描述了在ΔM2-2重组病毒株的情况下对该策略的意外限制。可以修饰F和/或G蛋白氨基酸序列以代表当前的流行株,其在趋异(divergent)G蛋白的情况下可能相关,或代表早期传代的临床分离株。可以将缺失或取代引入G蛋白中以获得改善的免疫原性或其他所需特性。例如,可以消除G蛋白中的CX3C fractalkine基序以改进免疫原性(Chirkova et al.J Virol 2013 87:13466-13479)。

[0089] 例如,在一些实施方案中,编码RSV的G蛋白的核苷酸序列可以用来自临床分离株A/Maryland/001/11的相应核苷酸序列替换。在一些实施方案中,编码RSV的F蛋白的核苷酸序列可以用来自临床分离株A/Maryland/001/11的相应核苷酸序列替换,例如,F001(SEQ ID NO:10)。

[0090] 在一些实施方案中,编码RSV蛋白的天然或天然存在的核苷酸序列可以用密码子优化的序列替换,所述密码子优化的序列被设计用于在选定的宿主,特别是人中增加表达。例如,在一些实施方案中,编码RSV的F蛋白的核苷酸序列可以用密码子优化的序列FBB(“FBB”)(SEQ ID NO:9)替换。在一些实施方案中,编码RSV的F蛋白的核苷酸序列可以用来自临床分离株A/Maryland/001/11的密码子优化序列(“F001BB”)(SEQ ID NO:11)替换。在一些实施方案中,编码RSV的G蛋白的核苷酸序列可以用来自临床分离株A/Maryland/001/11的密码子优化的核苷酸序列G001BB(SEQ ID NO:8)替换(“G001BB”)。

[0091] 本发明的另外方面涉及改变基因的位置或改变基因顺序以产生或修饰M2-2缺失突变体RSV。例如,可以单独缺失NS1,NS2,SH和G基因,或者可以一起缺失NS1和NS2基因,从而相对于病毒启动子改变每个下游基因的位置。例如,当NS1和NS2一起被缺失时,N从基因位置3移动到基因位置1,P从基因位置4移动到基因位置2,依此类推。或者,基因顺序内任何其他基因的缺失将仅影响位于更下游的那些基因的位置(相对于启动子)。例如,SH在野生型病毒中占据位置6,并且其缺失不影响位置5的M(或任何其他上游基因),而是相对于启动子将G从位置7移动到6。应该注意的是,基因缺失也可以(很少)在生物衍生的突变病毒中发生。例如,已在细胞培养物中充分传代的亚组B RSV自发地缺失SH和G基因(Karron等,Proc.Natl.Acad.Sci.USA 94:13961 13966,1997;通过引用并入本文)。

[0092] 基因顺序迁移修饰(即,将一个或多个基因移动到重组病毒基因组中的更靠近启动子-近端或启动子-远端位置的位置修饰)导致具有改变的生物学特性的病毒。例如,已显示同时缺乏NS1、NS2、SH、G、NS1和NS2,或同时缺乏SH和G的RSV在体外、体内或两者都减毒。具体地,G和F基因可以单独地和串联地迁移到相对于它们的野生型基因顺序更靠近启动子的位置。这两种蛋白质通常占据RSV基因顺序(NS1-NS2-N-P-M-SH-G-FM2-L)的位置7(G)和8(F)。在一些实施方案中,编码G蛋白和F蛋白的核苷酸序列的顺序可以相对于天然存在的顺序逆转。

[0093] 已知RSV F和G蛋白诱导RSV中和抗体,并且是主要的保护性抗原。F蛋白通常被认为是比G蛋白更有效的中和和保护性抗原。F在RSV株中也相对非常保守,而G蛋白可以实质上趋异。G的趋异是将RSV株分成两个抗原亚组A和B的主要因素(G和F的两个亚组之间分别有约～53％和～90％的氨基酸序列同一性)。本公开的工具和方法集中于亚组A的RSV株A2,但是可以容易地应用于任一亚组的其他株。

[0094] 在一些实施方案中,重组RSV株包含重组RSV基因组,其包含ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变与一种或多种上述突变的组合。在一些实施方案中,重组RSV毒株包

含重组RSV基因组，其包含已经用ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变以及一种或多种上述突变修饰的D46(SEQ ID NO:1)基因组。

[0095] 在一些实施方案中，重组株可以是基于D46的RSV株，包括“276”突变，并且还包括所公开的M2-2突变之一，例如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变。如实施例8中所讨论的，“276”突变包括以下核苷酸突变:C1099、1138A、1139G、1181G、1209G、5611A、5615A、5639G、6215C、6221C、6386T、7214C、7481T、7559A、7701G、10514T和13633A(相对于SEQ ID NO:1，这些突变如下:404C、779G、C1099缺失、1139A、1140G、1182G、1210G、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T和13634A)。基于ΔM2-2-HindIII的RSV毒株的包括“276”突变的示例性反基因组cDNA序列如SEQ ID NO:19所示。

[0096] 在一些实施方案中，重组RSV株包含基因组，其包含对应于与SEQ ID NO:1所示的反基因组cDNA序列至少90％相同(如至少95％相同或至少99％相同)的反基因组cDNA序列的核苷酸序列，其已修饰为包括如上所述的ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变之一，单独或组合本文提供的一种或多种减毒突变。

[0097] 在一些实施方案中，重组RSV株包含基因组，其包含如本文所述的cp和M2-2突变，和对应于与SEQ ID NO:1(D46序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0098] 在一些实施方案中，重组RSV株包含基因组，其包含如本文所述的ΔM2-2突变，和对应于与SEQ ID NO:2(D46/ΔM2-2序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0099] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的ΔM2-2-AclI突变，和对应于与SEQ ID NO:3(D46/ΔM2-2-AclI序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0100] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的ΔM2-2-HindIII突变，和对应于与SEQ ID NO:4(D46/ΔM2-2-HindIII序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0101] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的LID和ΔM2-2突变，和对应于与SEQ ID NO:5(LID/ΔM2-2序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0102] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的LID和ΔM2-2-AclI突变突变，和对应于与SEQ ID NO:6(LID/ΔM2-2-AclI序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0103] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的LID和ΔM2-2-HindIII突变，和对应于与SEQ ID NO:7(LID/ΔM2-2-HindIII序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0104] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的cp和ΔM2-2突变，和对应于与SEQ ID NO:15(D46/cp/ΔM2-2序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0105] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的6120、ΔM2-2和1030s突变，和对应于与SEQ ID NO:16(LID/ΔM2-2/1030s序列)至少90％相同、至少95％

相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0106] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的6120、cp和ΔM2-2突变，和对应于与SEQ ID NO:17(LID/cp/ΔM2-2序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0107] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的NS2、N、ΔM2-2-HindIII突变，和对应于与SEQ ID NO:4(D46/ΔM2-2-HindIII序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0108] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的NS2、N、ΔM2-2-HindIII突变，和对应于与SEQ ID NO:18(D46/NS2/N/ΔM2-2-HindIII序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0109] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的NS2、N、ΔM2-2-AclI突变，和对应于与SEQ ID NO:3(D46/ΔM2-2-AclII序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0110] 在一些实施方案中，重组RSV毒株包含基因组，其包含如本文所述的NS2、N和ΔM2-2-AclI突变，具有以下相对SEQ ID NO:1的位置的核苷酸突变：404C、779G、C1099缺失、1139A、1140G、1182G、1210G、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T和13634A；和对应于与SEQ ID NO:19(276序列)至少90％相同、至少95％相同和/或至少99％相同的反基因组cDNA序列的核苷酸序列。

[0111] 在一些实施方案中，重组RSV毒株包含基因组，其包含对应于下述任一项所述的正义序列的核苷酸序列：SEQ ID NO:2、SEQ ID NO:3、SEQ ID NO:4、SEQ ID NO:5、SEQ ID NO:6、SEQ ID NO:7、SEQ ID NO:15、SEQ ID NO:16、SEQ ID NO:17、SEQ ID NO:18或SEQ ID NO:19。

[0112] 在若干实施方案中，重组RSV的基因组包含如本文所讨论的一种或多种突变，并且重组RSV的基因组与D46RSV(SEQ ID NO:1)的基因组序列相比的任何剩余序列差异在生物学上是不重要的(例如，剩余的序列差异不包括对野生型基因组序列的如下改变，所述改变修饰已知的顺式作用信号或改变氨基酸编码，或可测量地影响病毒的体外复制或噬斑大小)。

[0113] 除了上述突变外，感染性M2-2缺失突变体(例如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)可以并入异源、编码或非编码核苷酸序列，所述序列来自任何RSV或RSV样病毒，例如人、牛、绵羊、鼠(小鼠的肺炎病毒)或禽类(火鸡鼻气管炎病毒)肺病毒，或来自另一种包膜病毒例如副流感病毒(PIV)。示例性异源序列包括来自一种人RSV株的RSV序列与来自不同人RSV株的序列的组合。或者，M2-2缺失突变体(例如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)可并入来自两个或更多个野生型或突变型人RSV亚组的序列，例如，人RSV亚组A和亚组B序列的组合。在另外的方面，一种或多种人RSV编码或非编码多核苷酸以来自异源RSV或非RSV病毒的对应序列取代，以产生新的减毒疫苗株。

[0114] 除了具有特定突变的重组RSV和本文所述的那些突变的组合之外，如本领域技术人员所理解的，可以进一步修饰所公开的病毒。例如，重组RSV可以将其一种或多种蛋白质缺失或以其他方式突变，或者可以将来自不同生物体的异源基因添加到基因组或反基因组中，使得重组RSV在感染细胞和复制时表达或并入该蛋白质。此外，本领域技术人员将理解，

已知对RSV具有影响的其他先前定义的突变可以与本文描述的任何突变中的一个或多个组合以产生具有期望的减毒或稳定性特征的重组RSV。

[0115] 在一些实施方案中，当单独使用或与另一种突变组合使用时，本文所述的突变可提供不同水平的病毒减毒，提供调节减毒和免疫原性之间平衡的能力，并提供比亲本病毒更稳定的基因型。

[0116] 关于所述病毒的核苷酸和氨基酸序列位置的序列编号，使用惯例由此给定病毒序列中的每个核苷酸或氨基酸残基保留其在原始的15,222-核苷酸生物wt株A2病毒(GenBank登录号M74568)中具有的序列位置编号，不论任何修饰。因此，尽管许多基因组含有导致核苷酸长度变化并且在某些情况下氨基酸长度变化的缺失和/或插入，但基因组和编码蛋白质中所有其他残基(核苷酸或氨基酸)的编号保持不变。还认识到，即使没有该惯例的权宜之计，通过序列比对以及开放阅读框的位置，众所周知的RNA特征，如基因起始和基因末端信号以及氨基酸序列特征的指导，本领域技术人员也可以容易地鉴定病毒基因组或蛋白质之间可能长度不同的相应序列位置。

[0117] 可以使用示例性重组毒株使用本文所述并在实施例中说明的方法，在细胞培养物中评估来自本公开中描述的那些的其他代表性病毒的感染性、复制动力学、产量、蛋白质表达效率和遗传稳定性。可以在啮齿动物和非人灵长类动物中评估其他代表性株的感染性、复制动力学、产量、免疫原性和遗传稳定性。虽然这些半允许系统可能不能可靠地检测复制中的每个差异，但是可以具体检测到实质性差异(例如，在RSV D46/ΔM2-2和LID/ΔM2-2之间，表4和5)。还可以在血清阴性儿童中直接评估重组株，而无需在成人和血清阳性儿童中进行在先的评估步骤。例如，这可以在例如10个疫苗接受者和5个安慰剂接受者的组中完成，其数量小，允许同时评估多个候选者。可以在免疫后立即评估候选人的疫苗病毒感染性、复制动力学、脱落、耐受性、免疫原性和遗传稳定性，并且可以在接下来的RSV季节对疫苗接种者进行监测，以确保安全性、RSV疾病和在RSV特异性血清抗体中的变化，如Karron, et al.2015,Science Transl Med 2015 7(312):312ra175所述，其全部内容并入本文。因此，对所选代表性病毒的分析可以提供相对快速的分类以缩小候选者以识别最佳候选。

[0118] 对蛋白质或肽的提及包括其天然存在的形式，以及这种蛋白质的任何片段、结构域或同源物。如本文所用，术语“同源物”用于指通过对天然存在的蛋白质或肽的次要修饰而不同于天然存在的蛋白质或肽(即“原型”或“野生型”蛋白质)，但保持天然存在形式的基本蛋白质和侧链结构的蛋白质或肽。这些变化包括但不限于：一个或几个氨基酸侧链的变化；一个或几个氨基酸的变化，包括缺失(例如蛋白质或肽的截短形式)、插入和/或取代；一个或几个原子的立体化学变化和/或次要衍生化，包括但不限于：甲基化、糖基化、磷酸化、乙酰化、豆蔻酰化、异戊烯化、棕榈酸化、酰胺化。与天然存在的蛋白质或肽相比，同源物可具有增强的，减少的或基本相似的性质。给定蛋白质的同源物可包含与参照蛋白的氨基酸序列至少约50％，或至少约55％，或至少约60％，或至少约65％，或至少约70％，或至少约75％，或至少约80％，或至少约85％，或至少约90％，或至少约95％，或至少约96％，或至少约97％，或至少约98％，或至少约99％相同(或以整数增量在45％至99％之间的任何百分比同一性)的氨基酸序列，或由其组成。

[0119] 在本发明的一个方面，来自一种RSV的所选基因区段，例如编码选定的蛋白质或蛋白质区域的基因区段(例如，细胞质尾部、跨膜结构域或胞外域、表位部位或区域、结合位点

或区域、活性位点或包含活性位点的区域等)可以取代来自相同或不同RSV或其他来源的对应基因区段,以产生与野生型或亲本RSV株相比具有所需表型变化的新型重组体。例如,这种类型的重组体可以表达嵌合蛋白,其具有与另一RSV的胞外域融合的一个RSV的细胞质尾和/或跨膜结构域。这种类型的其他示例性重组体表达重复的蛋白质区域,例如重复的免疫原性区域。如本文所用,"对应"基因、基因区段、蛋白质或蛋白质区域通常来自异源来源(例如,来自不同RSV基因,或代表不同RSV株中的相同(即同源或等位基因)基因或基因区段)。在该上下文中选择的典型对应物共享总体结构特征,例如,每个对应物可编码可比较的结构性"结构域",如细胞质结构域、跨膜结构域、胞外域、结合位点或区域、表位位点或区域等。对应结构域和它们的编码基因区段包含具有一系列大小和氨基酸(或核苷酸)序列变异的物种的组合,其范围由结构域或基因区段变体之间的共同生物活性限定。例如,由本发明中的对应基因区段编码的两个选定的蛋白质结构域可以共享基本相同的定性活性,例如提供跨膜功能、特异性结合活性、免疫学识别位点等。更典型地,在对应物之间如在所选蛋白质区段或蛋白质之间共享特定的生物活性在定量方面将基本相似,即它们在各自的定量活性谱中不会变化超过30%,优选不超过20%,更优选不超过5-10%。

[0120] 在本发明的另一方面,由cDNA表达的基因组或反基因组产生的感染性RSV可以是任何RSV或RSV样株,例如人、牛、鼠等,或任何肺病毒或间质肺病毒,例如,小鼠的肺炎病毒或禽类间质肺病毒。为了产生保护性免疫应答,RSV株可以是被免疫的受试者中内源的,如用于免疫人的人RSV。然而,内源RSV的基因组或反基因组可以被修饰以表达来自不同来源的组合的RSV基因或基因区段,例如来自不同RSV物种、亚组或株的基因或基因区段的组合,或来自RSV和另一种呼吸道病原体如人副流感病毒(PIV)的基因或基因区段的组合(参见,例如,Hoffman et al.J.Virol.71:4272-4277(1997);Durbin et al.Virology 235(2):323-32(1997);Murphy et al.1997年5月23日提交的美国专利申请序列号60/047,575)和用于产生感染性PIV克隆的以下质粒:p3/7(131)(ATCC 97990);p3/7(131)2G(ATCC 97889);和p218(131)(ATCC 97991),其各自根据布达佩斯条约的条款于1998年4月18日保藏于美国典型培养物保藏中心(ATCC),10801University Blvd.,Manassas,Va.20110-2209,USA.,并授予上述确定的登录号。

[0121] 在本发明的某些实施方案中,提供了重组RSV,其中人RSV的个体内部基因被例如牛或其他RSV对应物替换,或被来自另一种呼吸道病原体例如PIV的对应物或外源基因替换。在该上下文中RSV基因或基因区段的取代,缺失等可包括NS1、NS2、N、P、M、SH和L基因中的一种或多种的部分或全部,或M2-1开放阅读框,或G和F基因的非免疫原性部分。而且,人RSV顺式作用序列,例如启动子或转录信号,可以用例如它们的牛RSV对应物替换。相反地,提供了通过将人减毒基因或顺式作用序列插入牛RSV基因组或反基因组背景来产生活减毒牛RSV的方法。

[0122] 因此,用于对人施用的感染性重组RSV可以是经修饰以含有来自例如牛RSV或PIV的基因的人RSV,例如用于减毒的目的。例如,通过插入来自PIV基因或基因区段,提供了针对PIV和RSV的二价疫苗。或者,可以修饰异源RSV种类、亚组或株,或不同的呼吸道病原体如PIV,例如,以包含编码表位或蛋白质的基因,所述表位或蛋白质引发针对人RSV感染的保护。例如,人类RSV糖蛋白基因可以替代牛糖蛋白基因,从而产生牛RSV,其现在具有人RSV表面糖蛋白,并且由于剩余的牛遗传背景而在人宿主中保留有限的复制能力,其在人类中引

发针对人RSV株的保护性免疫应答。

[0123] 分析其他类型的减毒突变并将其纳入感染性RSV用于疫苗开发的能力扩展到RSV克隆的靶向变化的广泛组合。例如，可以消除或以其他方式修饰对生长不必要的任何RSV基因，以产生对毒力、发病机理、免疫原性和其他表型特征的所需效果。此外，可以在重组RSV基因组或反基因组中产生多种其他遗传改变，用于单独或与从生物学衍生的突变RSV采用的一种或多种减毒点突变一起并入感染性重组RSV。

[0124] 如本文所用，“异源基因”是指取自不同RSV株或类型或非RSV来源的基因。这些异源基因可以全部或部分插入，基因顺序改变，基因重叠被去除，RSV基因组启动子被其反基因组对应物取代，基因部分被去除或取代，甚至整个基因被缺失。可以对序列进行不同的或另外的修饰以促进操作，如在各种基因间区域(例如，G和F基因之间的独特StuI位点)或其他地方插入独特的限制性位点。可以去除未翻译的基因序列以增加插入外来序列的能力。

[0125] 涉及本发明的重组RSV中的整个病毒基因或基因区段的变化的缺失、插入、取代和其他突变产生高度稳定的疫苗候选物，在免疫抑制个体的情况下其可能是相关的。这些突变中的许多将导致所得疫苗株的减毒，而其他突变将指定不同类型的所需表型变化。例如，已知某些病毒基因编码特异性干扰宿主免疫的蛋白(参见，例如，Kato et al.,EMBO.J.16:578-87(1997))。预期疫苗病毒中此类基因的消除减少毒力和发病和/或改进免疫原性。

[0126] 本发明的RSV内的其他突变涉及用来自反基因组的其对应物替换基因组的3’末端，其与RNA复制和转录的变化相关。此外，基因间区域(Collins et al.,Proc.Natl.Acad.Sci.USA 83:4594-4598(1986))可以缩短或延长或改变序列内容，并且天然存在的基因重叠(Collins et al.,Proc.Natl.Acad.Sci.USA 84:5134-5138(1987))可通过本文所述的方法除去或改变为不同的基因间区域。

[0127] 在另一个实施方案中，选择的RSV基因的翻译起始位点(优选包括-3位核苷酸)周围的序列被单独修饰或与引入上游起始密码子组合进行修饰，以通过指定的翻译上调或下调调节RSV基因表达。

[0128] 或者，或与本文公开的其他RSV修饰组合，可通过改变所选病毒基因的转录GS信号来调节RSV基因表达。在一个示例性实施方案中，修饰NS2的GS信号以包括限定的突变以在病毒复制上叠加ts限制。

[0129] 本发明中的另外的RSV克隆并入了对转录GE信号的修饰。例如，提供RSV克隆，其替代或突变NS1和NS2基因的GE信号用于N基因的GE信号，导致通读mRNA水平降低和来自下游基因的蛋白质表达增加。得到的重组病毒表现出增加的生长动力学和增加的斑块大小，提供了通过修饰RSV基因组中的顺式作用调节元件改变RSV生长特性的一个实例。

[0130] 另一方面，可以通过修饰G mRNA来增加G蛋白的表达。G蛋白表达为膜结合和分泌形式，后一形式通过G基因翻译开放阅读框内起始位点的翻译起始表达。分泌形式可占表达的G蛋白的一半。单独或与改变上游起始位点的序列背景一起消除内部起始位点(例如，通过序列改变、缺失等)，产生G蛋白表达的所需变化。消除G蛋白的分泌形式也将改进宿主对示例性重组RSV的免疫应答的质量，因为G蛋白的可溶形式被认为充当捕获中和抗体的“诱饵”。此外，可溶性G蛋白由于其优先刺激Th2偏向响应而涉及增强的免疫病理学。

[0131] 在相关方面，可以在转录水平修饰RSV基因表达水平。在一个方面，RSV基因图谱中所选基因的位置可以改变为更靠近启动子-近端或启动子-远端的位置，由此基因的表达效

率会更高或更低。根据该方面，可以实现对特定基因的表达的调节，使基因表达与野生型水平相比减少或增加两倍，更通常四倍，高达十倍或更多。在一个实例中，NS2基因(RSV基因图谱中的第二顺序)的位置被SH基因取代(顺序为第六)，产生预期的NS2表达的降低。由于位置变化导致的所选RSV基因的表达增加可以高达10倍、30倍、50倍、100倍或更多，通常伴随相互位置取代基因的表达水平的相应降低。

[0132] 在一些示例性实施方案中，F和G基因可以单独或一起转座至(重组)RSV基因图谱内的更靠近启动子-近端或启动子-远端的位点，以分别实现更高或更低水平的基因表达。这些和其他转座变化产生具有减毒表型的新型RSV克隆，例如由于参与RNA复制的所选病毒蛋白的表达降低。在其他实施方案中，可以方便地修饰可用于疫苗制剂的RSV以适应流行病毒中的抗原漂移。通常，修饰将在G和/或F蛋白中。整个G或F基因或编码其特定免疫原性区域的区段通过替换感染性克隆中的相应区域或通过添加一个或多个基因拷贝而并入RSV基因组或反基因组cDNA中，使得呈现数个抗原形式。

[0133] 然后将由修饰的RSV cDNA产生的子代病毒用于针对新出现的株的疫苗接种方案中。此外，包含RSV亚组B的G蛋白基因作为基因添加将扩大响应以覆盖人群中存在的相对多样的亚组A和B毒株的更广的谱。

[0134] 还可以根据本文公开的方法和组合物工程化本发明的感染性RSV克隆，以增强其免疫原性并诱导比用野生型RSV或不完全减毒亲本病毒或克隆感染所提供的更高的保护水平。例如，可以通过编码RSV基因组或反基因组的多核苷酸序列中的适当核苷酸变化来添加来自异源RSV株或类型，或来自非RSV来源例如PIV的免疫原性表位。还可以工程化重组RSV以鉴定和消除(例如，通过氨基酸插入、取代或缺失)与不希望的免疫病理反应相关的表位。在其他实施方案中，额外的基因可以插入RSV基因组或反基因组中或在其附近，其处于独立的一组转录信号的控制下。感兴趣的基因可包括但不限于编码细胞因子(例如，IL-2至IL-15，尤其是IL-2、IL-6和IL-12等)、γ-干扰素的那些，并包括编码细胞因子(例如，IL-2至IL-15，尤其是IL-2，IL-6和IL-12等)，γ-干扰素和富含T辅助细胞表位的蛋白质的那些。额外的蛋白质可以作为单独的蛋白质或作为从RSV蛋白质之一(例如SH)的第二拷贝工程化的嵌合体表达。这提供了在数量上和质量上修饰和改进针对RSV的免疫应答的能力。

[0135] 除了上述对重组RSV的修饰之外，可以对RSV克隆进行不同或额外的修饰以促进操作，如在各种基因间区域或其他地方插入独特的限制性位点(例如，G和F基因之间的独特Stul位点)。可以去除未翻译的基因序列以增加插入外来序列的能力。

[0136] 通过各种众所周知的方法可以实现将前述定义的突变引入感染性RSV克隆。“感染性克隆”是指cDNA或其合成或其他产物，其可以转录成能够产生感染性病毒的基因组或反基因组RNA。术语“感染性”是指能够在培养的细胞或动物或人宿主中复制以产生能够具有相同活性的子代病毒或病毒结构的病毒或病毒结构。因此，可以通过常规技术(例如定点诱变)将确定的突变引入基因组或反基因组的cDNA拷贝中。使用反基因组或基因组cDNA亚片段组装完整的反基因组或基因组cDNA是本领域普通技术人员所熟知的，并且具有可以分别操作每个区域的优点(较小的cDNA比较大的更易于操作)然后很容易组装成完整的cDNA。因此，完整的反基因组或基因组cDNA或其任何亚片段可用作寡核苷酸定向诱变的模板。然后可以将突变的亚片段组装成完整的反基因组或基因组cDNA。突变可以从单核苷酸变化到含有一个或多个基因或基因组区域的大cDNA片段的替换。

[0137] 重组RSV可以通过编码RSV基因组RNA的cDNA的细胞内共表达产生，以及产生转录、复制核衣壳所必需的那些病毒蛋白。编码其他RSV蛋白质的质粒也可包含这些必需蛋白质。或者，RNA可以在体外转录反应中合成并转染到培养的细胞中。

[0138] 因此，本文还描述了分离的多核苷酸，其编码所述突变病毒，构成所述基因组或反基因组，表达所述基因组或反基因组，或编码可用于体外制备重组RSV的各种蛋白质。包含本文所述任何SEQ ID NO的序列的多核苷酸包括在本发明中。进一步包括的是包含由任何上述序列组成或基本上由其组成的序列的多核苷酸，与上述任何SEQ ID NO具有至少约70、71、72、73、74、75、76、77、78、79、80、81、82、83、84、85、86、87、88、89、90、91、92、93、94、95、96、97、98、99或100的百分比同一性(或其间的任何百分比同一性)的序列，以及与上述分子杂交或是上述分子的互补序列的多核苷酸。

[0139] 这些多核苷酸可包含在载体内或由载体表达，以产生重组RSV。因此，用分离的多核苷酸或载体转染的细胞也在本发明的范围内并在本文中举例说明。

[0140] 在本发明的相关方面，提供了用于产生具有减毒、M2-2缺失突变的分离的感染性重组RSV(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)的组合物(例如，并入RSV编码cDNA的分离的多核苷酸和载体)和方法。本发明的这些方面包括新颖的，分离的多核苷酸分子和并入此类分子的载体，所述分子包含如本文所述进行修饰的RSV基因组或反基因组。还提供了相同或不同的表达载体，其包含一种或多种编码RSV蛋白的分离的多核苷酸分子。这些蛋白质也可以直接从基因组或反基因组cDNA中表达。载体优选在细胞或无细胞裂解物中表达或共表达，从而产生感染性M2ORF2缺失或敲除突变体RSV颗粒或亚病毒颗粒。

[0141] 在一个方面，提供产生一种或多种纯化的RSV蛋白的方法，其涉及在允许RSV在感染细胞中繁殖的条件下用重组RSV株感染允许RSV感染的宿主细胞。在培养物中复制一段时间后，裂解细胞并从中分离重组RSV。在分离病毒后纯化一种或多种所需的RSV蛋白，产生一种或多种RSV蛋白用于疫苗、诊断和其它用途。

[0142] 用于产生M2-2缺失突变体(例如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)的上述方法和组合物产生感染性病毒或亚病毒颗粒或其衍生物。感染性病毒与真正的RSV病毒颗粒相当，并且同其一样具有感染性。它可以直接感染新鲜细胞。感染性亚病毒颗粒通常是病毒颗粒的亚组分，其可以在适当条件下引发感染。例如，含有基因组或反基因组RNA和N、P、L和M2-1蛋白的核衣壳是亚病毒颗粒的一个实例，如果引入细胞的细胞质中它可引发感染。本发明提供的亚病毒颗粒包括缺少一种或多种蛋白质、蛋白质区段或对感染性不是必需的其它病毒组分的病毒颗粒。

[0143] 在其他实施方案中，本发明提供含有表达载体的细胞或无细胞裂解物，所述表达载体包含编码如上所述的编码M2-2缺失突变体(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)RSV基因组或反基因组的分离的多核苷酸分子，和包含编码RSV的N、P、L和RNA聚合酶延伸因子蛋白的一种或多种分离的多核苷酸的表达载体(相同或不同的载体)。这些蛋白质中的一种或多种也可以从基因组或反基因组cDNA中表达。表达后，基因组或反基因组和N、P、L和RNA聚合酶延伸因子蛋白结合在一起产生感染性RSV病毒或亚病毒颗粒。

[0144] 本发明的重组RSV可用于各种组合物中，以在易受RSV感染的宿主中产生针对RSV的所需免疫应答。如本文公开的减毒的M2-2缺失突变体(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)RSV株能够在受感染的人宿主中引发保护性免疫应答，而足以减毒以免在

免疫的宿主中引起严重呼吸道疾病的不可接受的症状。减毒病毒或亚病毒颗粒可以存在于细胞培养上清液中，从培养物中分离，或部分或完全纯化。病毒也可以是冻干的，并且可以根据需要与各种其他组分组合用于储存或递送至宿主。

[0145] 另一方面，M2-2缺失突变体(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)可用作其他病原体特别是呼吸道病原体如副流感病毒(PIV)的保护性抗原的“载体”。例如，可以工程化具有M2-2缺失的重组RSV(如ΔM2-2、ΔM2-2-AclI或ΔM2-2-HindIII突变体)，其并入编码来自PIV的保护性抗原的序列以产生感染性、减毒疫苗病毒。

[0146] 在相关方面，本发明提供了刺激个体免疫系统以在哺乳动物受试者中引发针对RSV的免疫应答的方法。该方法包括施用在生理学上可接受的载体和/或佐剂中具有免疫原性足量的如本文所述的减毒M2-2缺失突变体RSV的免疫原性制剂。

[0147] 本发明还提供了新的疫苗，其包含生理学上可接受的载体和/或佐剂和分离的减毒M2-2缺失突变体RSV颗粒或亚病毒颗粒。在优选的实施方案中，疫苗包含具有至少一种；且优选两种或更多减毒突变或如上文所述的其他核苷酸修饰的M2-2缺失突变体RSV以实现减毒和免疫原性的适当平衡。

[0148] 为了从本文提供的重组RSV株的宿主中选择候选疫苗病毒，根据众所周知的方法测定活力、体外有效复制、体内减毒、免疫原性和表型稳定性的标准。在本发明的疫苗中最需要的病毒应该保持活力，应该在允许的条件下在体外充分复制以使疫苗制造成为可能，应该具有稳定的减毒表型，应该是良好耐受的，应该在免疫的宿主中表现出复制(尽管水平较低)，并且应该在足以赋予对由野生型病毒感染引起的严重疾病的保护的疫苗中有效引发免疫应答的产生。

[0149] 为了繁殖RSV病毒用于疫苗用途和其他目的，可以使用许多允许RSV生长的细胞系。RSV生长在各种人和动物细胞中。用于繁殖用于疫苗的减毒RS病毒的优选细胞系包括DBSFRhL-2、MRC-5和Vero细胞。通常用上皮细胞系如Vero细胞实现最高的病毒产量。细胞通常以约0.001至1.0或更高的感染复数接种病毒，并在允许病毒复制的条件下培养，例如在约30-37℃和约3-10天，或只要是病毒达到足够的滴度所必需的条件。温度敏感病毒通常使用32℃作为“允许温度”生长。病毒从细胞培养物中除去并通常通过众所周知的澄清程序(例如离心)与细胞组分分离，并且可以根据需要使用本领域技术人员已知的程序进一步纯化。

[0150] 已经如本文所述减毒的RSV可以在各种众所周知且通常接受的体外和体内模型中进行测试，以确认足够的减毒，对表型逆转的抗性和疫苗使用的免疫原性。在体外测定中，测试经修饰的病毒，其可以是多重减毒的，生物学衍生的或重组的RSV，用于测试病毒复制的温度敏感性或“ts表型”和小斑块表型。在RSV感染的动物模型中进一步测试经修饰的病毒。已经描述了多种动物模型(例如鼠、棉鼠和灵长类)，这些动物模型是本领域技术人员已知的。

[0151] 根据前面的描述并基于以下实施例，本发明还提供了用于疫苗使用的分离的感染性RSV组合物。作为疫苗组分的减毒病毒是分离的并且通常是纯化的形式。分离意指RSV处于非野生型病毒的天然环境如受感染个体的鼻咽。更一般地，分离意指包括减毒病毒作为细胞培养物或其他人工培养基的组分。例如，本发明的减毒RSV可以由感染的细胞培养物产生，与细胞培养物分离并加入稳定剂中。

[0152] 本发明的RSV疫苗含有如本文所述产生的免疫原性有效量的RSV作为活性成分。生物衍生的或重组RSV可直接用于疫苗制剂中。可以将生物学衍生或重组修饰的病毒与生理学上可接受的载体和/或佐剂一起引入宿主中。有用的载体是本领域熟知的，包括例如水、缓冲水、0.4％盐水、0.3％甘氨酸、透明质酸等。得到的水溶液可以按原样包装使用，或者以冷冻形式使用，在使用前解冻，或冻干，冻干制剂在施用前与无菌溶液混合，如上所述。该组合物可含有接近生理条件所需的药学上可接受的辅助物质，包括但不限于pH调节剂和缓冲剂、张力调节剂、润湿剂等，例如乙酸钠、乳酸钠、氯化钠、氯化钾、氯化钙、蔗糖、硫酸镁、磷酸盐缓冲剂、HEPES(4-(2-羟乙基)-1-哌嗪乙磺酸)缓冲剂、脱水山梨糖醇单月桂酸酯和三乙醇胺油酸酯。可接受的佐剂包括不完全弗氏佐剂、磷酸铝、氢氧化铝或明矾，它们是本领域熟知的材料。优选的佐剂还包括Stimulon™QS-21(Aquila Biopharmaceuticals,Inc.,Worchester,Mass.)、MPL™(3-0-脱酰单磷酰脂质A;RIBI ImmunoChem Research,Inc.,Hamilton,Mont.)和白细胞介素-12(Genetics Institute,Cambridge,Mass)。

[0153] 在用RSV疫苗组合物免疫后，宿主通过产生对RSV病毒蛋白(例如F和G糖蛋白)特异性的抗体来响应疫苗。此外，诱导了天然和细胞介导的免疫应答，其可提供抗病毒效应物以及调节免疫应答。作为接种疫苗的结果，宿主变得至少部分或完全免疫RSV感染，或对形成中度或严重RSV疾病，特别是下呼吸道疾病有抗性。

[0154] 将含有本发明的减毒RSV的疫苗组合物以“免疫原性有效剂量”施用至易受RSV感染或处于RSV感染风险的受试者，该免疫原性有效剂量足以诱导或增强个体对RSV的免疫应答能力。RSV疫苗组合物可以通过任何合适的方法施用，包括但不限于经由注射、气溶胶递送、鼻喷雾、鼻滴剂、口服接种或局部应用。在人受试者的情况下，根据公认的人RSV疫苗方案(Karron et al.JID 191:1093-104,2005)施用本发明的减毒病毒。简而言之，成人或儿童经由液滴以免疫原性有效剂量鼻内接种RSV疫苗，通常体积为0.5ml生理学上可接受的稀释剂或载体。与使用非复制型疫苗的肠胃外免疫相比，这具有简单和安全的优点。它还提供对局部呼吸道免疫的直接刺激，其在抗RSV中起主要作用。此外，这种疫苗接种方式有效地绕过了RSV特异性母源血清抗体的免疫抑制作用，这种抗体通常存在于非常年轻的人群中。此外，虽然胃肠外施用RSV抗原有时可能与免疫病理学并发症有关，但尚未观察到活病毒。

[0155] 在一些实施方案中，疫苗可以鼻内或皮下或肌肉内施用。在一些实施方案中，它可以施用于上呼吸道。这可以通过任何合适的方法进行，包括但不限于喷雾，液滴或气溶胶输送。通常，将组合物施用于针对RSV的抗体的血清阴性或具有针对RSV的经胎盘获得的亲本抗体的个体。

[0156] 在所有受试者中，所施用的RSV疫苗的精确量和施用时机和重复将由各种因素决定，包括患者的健康状况和体重、施用方式、制剂的性质等。剂量通常每位患者约$3.0\log_{10}$至约$6.0\log_{10}$噬斑形成单位(“PFU”)或更多病毒，更常见的是每位患者约$4.0\log_{10}$至$5.0\log_{10}$PFU病毒。在一个实施方案中，每个患者可以在婴儿期间施用约$5.0\log_{10}$至$6.0\log_{10}$PFU，例如在1至6个月大之间施用，并且可以在2-6个月或更长时间之后施用一个或多个额外的加强剂量。在另一个实施方案中，在约2、4和6个月大时(这是许多其他儿童疫苗的推荐施用时间)，小婴儿可以给予每名患者约$5.0\log_{10}$至$6.0\log_{10}$PFU的剂量。在另一个实施方案中，可以在约10-15个月大时施用另外的加强剂量。在任何情况下，疫苗制剂应提供足以有效刺激或诱导抗RSV免疫应答的量(“有效量”)的本发明的减毒RSV。

[0157] 在一些实施方案中，疫苗可包含减毒的M2-2缺失病毒，其引发针对单个RSV株或抗原亚组例如A或B或针对多种RSV株或亚组的免疫应答。在这方面，M2-2缺失突变体RSV可以在疫苗制剂中与其他RSV疫苗株或具有不同免疫原性特征的亚组组合，以更有效地针对一种或多种RSV株或亚组进行保护。它们可以在疫苗混合物中施用，或者在协调的治疗方案中单独施用以引发针对一种RSV株或针对多种RSV株或亚组的更有效的保护。

[0158] 产生的免疫应答可以通过多种方法表征。这些包括采集鼻洗液或血清样品用于分析RSV特异性抗体，其可通过包括但不限于补体固定、噬斑中和、酶联免疫吸附测定、荧光素酶免疫沉淀测定和流式细胞术的测试来检测。此外，可以通过测定鼻洗液或血清中的细胞因子测定、来自任一来源的免疫细胞的ELISPOT、定量RT-PCR或鼻洗液或血清样品的微阵列分析，以及再刺激来自鼻洗液或血清的免疫细胞(通过体外再次暴露于病毒抗原并分析由流式细胞术测量的细胞因子、表面标志物或其他免疫相关物的产生或展示，或针对展示RSV抗原的指示剂靶细胞的细胞毒活性)来检测免疫应答。在这方面，还监测个体的上呼吸道疾病的体征和症状。

[0159] 疫苗病毒的减毒水平可以通过例如量化免疫宿主呼吸道中存在的病毒量并将其与野生型RSV或已评估作为候选疫苗株的其他减毒RS病毒产生的量进行比较来确定。例如，与野生型病毒的复制水平相比，本发明的减毒病毒在高易感的宿主(例如黑猩猩)的上呼吸道中具有更大程度的复制限制(例如10-至1000-倍更少)。为了进一步减少与上呼吸道病毒复制有关的鼻漏的发展，理想的疫苗候选病毒应在上呼吸道和下呼吸道中都表现出有限的复制水平。然而，本发明的减毒病毒在人体中应具有足够的感染性和免疫原性，以赋予接种疫苗的个体保护。确定感染宿主鼻咽中RSV水平的方法在文献中是众所周知的。通过抽吸或冲洗鼻咽分泌物和通过组织培养或其他实验室程序定量的病毒获得标本。参见，例如，Belshe et al.,J.Med.Virology 1:157-162(1977),Friedewald et al.,J.Amer.Med.Assoc.204:690-694(1968);Gharpure et al.,J.Virol.3:414-421(1969);and Wright et al.,Arch.Ges.Virusforsch.41:238-247(1973)。可以方便地在宿主动物例如黑猩猩的鼻咽中测量病毒。

[0160] 其他实施方案

[0161] 项1.编码具有减毒表型的重组呼吸道合胞病毒(RSV)变体的分离的多核苷酸分子，其包含RSV基因组或反基因组序列，其中

[0162] (a)所述RSV基因组或反基因组通过M2-2ORF中对应包含位于SEQ ID NO:1的8189-8429位的241个核苷酸的缺失的缺失组合SEQ ID NO:1的位置T8161、T8167和T8179的突变来修饰；或

[0163] (b)所述RSV基因组或反基因组通过M2-2ORF中对应包含位于SEQ ID NO:1的8203-8436位的234个核苷酸的缺失的缺失组合SEQ ID NO:1中8198A和8200G的存在来修饰；或

[0164] (c)所述RSV基因组或反基因组通过M2-2ORF中包含位于SEQ ID NO:1的8203-8436位的234个核苷酸的缺失的缺失组合SEQ ID NO:1中8198A和8199G的存在来修饰。

[0165] 项2.项1的分离的多核苷酸分子，其中a和b中记载的RSV基因组或反基因组具有由与SEQ ID NO:1所示序列至少90％相同的序列表示的正义序列。

[0166] 项3.项1或2的分离的多核苷酸分子，其中RSV基因组或反基因组通过缺失位于SEQ ID NO:1的4499-4610位的112个核苷酸组合SEQ ID NO:1的突变C4489T、C4492T、A4495T、

A4497G和G4498A进一步修饰(“6120”)。

[0167] 项4.编码具有减毒表型的重组呼吸道合胞病毒(RSV)变体的分离的多核苷酸分子,其包含RSV基因组或反基因组,

[0168] 其具有由与SEQ ID NO:1至少90％相同的序列表示的正义序列,其中RSV基因组或反基因组通过M2-2ORF中的缺失修饰,所述缺失对应于包含位于SEQ ID NO:1的8203-8436位的234个核苷酸的缺失,

[0169] 其中RSV基因组或反基因组通过缺失位于SEQ ID NO:1的4499-4610位的112个核苷酸组合SEQ ID NO:1的突变C4489T、C4492T、A4495T、A4497G和G4498A进一步修饰。

[0170] 项5.项1、2、3或4的分离的多核苷酸分子,其中通过对SEQ ID NO:1引入一个或多个以下变化进一步修饰RSV基因组或反基因组:

[0171] 编码RSV的N蛋白中的V267I、F蛋白中的E218A和T523I和L蛋白中的C319Y和H1690Y的氨基酸取代的突变(“cp”);

[0172] 编码RSV的F蛋白中编码氨基酸取代K66E和Q101P的突变(“HEK”);

[0173] 编码RSV的SH蛋白缺失的位于SEQ ID NO:1的4198-4616位的419个核苷酸的缺失(ΔSH);

[0174] 编码RSV的NS2蛋白中的K51R氨基酸取代的突变(“NS2”);

[0175] 编码RSV的N蛋白中的T24A氨基酸取代的突变(“N”);

[0176] 将编码RSV的G蛋白的核苷酸序列取代为编码来自临床分离株A/Maryland/001/11的G蛋白的相应密码子优化的核苷酸序列;

[0177] 将编码RSV的F蛋白的核苷酸序列取代为编码来自临床分离株A/Maryland/001/11的F蛋白的相应核苷酸序列;或编码来自临床分离株A/Maryland/001/11的F蛋白的相应密码子优化的核苷酸序列;或密码子优化序列FBB(“FBB”);和

[0178] 将编码SEQ ID NO:1中RSV的G蛋白和F蛋白的核苷酸序列的顺序逆转。

[0179] 项6.项1(a)或2的分离的多核苷酸分子,其包含SEQ ID NO:2的核苷酸序列。

[0180] 项7.项1(b)或2的分离的多核苷酸分子,其包含SEQ ID NO:3的核苷酸序列。

[0181] 项8.项1(c)的分离的多核苷酸分子,其包含SEQ ID NO:4的核苷酸序列。

[0182] 项9.项3的分离的多核苷酸分子,其包含SEQ ID NO:5的核苷酸序列。

[0183] 项10.项3或4的分离的多核苷酸分子,其包含SEQ ID NO:6的核苷酸序列。

[0184] 项11.项3或4的分离的多核苷酸分子,其包含SEQ ID NO:7的核苷酸序列。

[0185] 项12.项5的分离的多核苷酸分子,其中修饰的RSV基因组或反基因组包含选自下组的突变组合:

[0186] cp/ΔM2-2、cp/ΔM2-2/HEK、ΔM2-2/1030s、NS2/N/ΔM2-2、NS2/ΔM2-2、N/ΔM2-2、NS2/N/ΔM2-2-AclI、ΔSH/ΔM2-2、cp/ΔSH/ΔM2-2、6120/cp/ΔM2-2、6120/ΔM2-2/1030s、6120/NS2/N/ΔM2-2、6120/G001BB/FBB/ΔM2-2、6120/FBB/G001BB/ΔM2-2、6120/G001BB/F/ΔM2-2、6120/G/FBB/ΔM2-2、6120/G/FBB/HEK/ΔM2-2、6120/G/FBB/cp/HEK/ΔM2-2、6120/FBB/G/ΔM2-2、6120/G001BB/F001BB/ΔM2-2、6120/NS2/ΔM2-2、6120/N/ΔM2-2、6120/NS2/N/ΔM2-2-Acl-I、NS2/N/ΔM2-2-HindIII和6120/NS2/N/ΔM2-2-HindIII。

[0187] 项13.项1的分离的多核苷酸分子,其中所述RSV基因组或反基因组包含选自下组的序列SEQ ID NO:2、SEQ ID NO:3和SEQ ID NO:4,其进一步通过在SEQ ID NO:2、SEQ ID

NO:3和SEQ ID NO:4中引入一种或多种下述核苷酸取代修饰:404C、779G、1099T、1139A、1140G、1182G、1210G、1939A、5612A、5616A、5640G、6216C、6222C、6387T、7215C、7482T、7560A、7702G、10515T、13634A、13901T。

[0188] 项14.项1-12中任一项的分离的多核苷酸分子,其进一步包含先前表征的RSV突变或缺失。

[0189] 项15.包含项1-13中任一项的分离的多核苷酸分子的载体。

[0190] 项16.包含项1-13中任一项的分离的多核苷酸分子的细胞。

[0191] 项17.药物组合物,其包含免疫有效量的由项1-13中任一项的分离的多核苷酸分子编码的重组RSV变体。

[0192] 项18.一种针对RSV免疫接种受试者的方法,包括施用项16的药物组合物。

[0193] 项18.项17的方法,其中所述药物组合物鼻内施用。

[0194] 项20.项17的方法,其中所述呼吸道合胞病毒经由注射、气溶胶输送、鼻喷雾或鼻滴剂施用。

[0195] 示例性序列

[0196] D46的反基因组cDNA序列(SEQ ID NO:1)

[0197] ACGGGAAAAAATGCGTACAACAAACTTGCATAAACCAAAAAAATGGGGCAAATAAGAATTTGATAAGTA
CCACTTAAATTTAACTCCCTTGGTTAGAGATGGGCAGCAATTCATTGAGTATGATAAAAGTTAGATTACAAAATTTG
TTTGACAATGATGAAGTAGCATTGTTAAAAATAACATGCTATACTGATAAATTAATACATTTAACTAATGCTTTGGC
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ATAATAATATTGTAGTAAAATCCAATTTCACAACAATGCCAGTACTACAAAATGGAGGTTATATATGGGAAATGATG
GAATTAACACATTGCTCTCAACCTAATGGTCTACTAGATGACAATTGTGAAATTAAATTCTCCAAAAAACTAAGTGA
TTCAACAATGACCAATTATATGAATCAATTATCTGAATTACTTGGATTTGATCTTAATCCATAAATTATAATTAATA
TCAACTAGCAAATCAATGTCACTAACACCATTAGTTAATATAAAACTTAACAGAAGACAAAAATGGGGCAAATAAAT
CAATTCAGCCAACCCAACCATGGACACAACCCACAATGATAATACACCACAAAGACTGATGATCACAGACATGAGAC
CGTTGTCACTTGAGACCATAATAACATCACTAACCAGAGACATCATAACACACAAATTTATATACTTGATAAATCAT
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CAAAGTAGGAAGCACTAAATATAAAAAATATACTGAATACAACACAAAATATGGCACTTTCCCTATGCCAATATTCA
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[0202] D46/ΔM2-2-HindIII的反基因组cDNA序列(SEQ ID NO:4)

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[0204] LID/ΔM2-2的反基因组cDNA序列(SEQ ID NO:5)

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[0206] LID/ΔM2-2-AclI的反基因组cDNA序列(SEQ ID NO:6)

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[0210] 编码G001BB的多核苷酸序列(SEQ ID NO:8)

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[0212] 编码FBB的多核苷酸序列(SEQ ID NO:9)

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[0214] 编码F001的多核苷酸序列(SEQ ID NO:10)

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[0216] 编码F001BB的多核苷酸序列(SEQ ID NO:11)

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[0218] D46/cp/ΔM2-2的反基因组cDNA序列(SEQ ID NO:15)

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[0220] LID/ΔM2-2/1030s的反基因组cDNA序列(SEQ ID NO:16)

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[0226] RSV 276基因组的反基因组cDNA序列(SEQ ID NO:19)

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[0228] 总之,本公开中描述的材料、信息和方法提供了一系列具有分级减毒表型的减毒株,并且提供了基于临床基准选择合适的疫苗候选毒株的指导。提供以下实施例是为了说明而非限制。

实施例

[0229] 1.本公开中举例说明的重组RSV株衍生自称为D46的wt株A2的重组形式(Collins,

et al.1995.Proc Natl Acad Sci USA 92:11563-11567)。D46的完整核苷酸序列显示为SEQ ID NO:1。RSV MEDI/ΔM2-2病毒不衍生自D46。

[0230] 2.在下面的实施例中,当病毒名称包括术语“LID”或“6120”时,这表示其骨架包含图3中所示的“6120”突变。

[0231] 3.本文通过列出其中存在的突变的组合来命名病毒。在病毒名称中使用符号“/”(如在RSV D46/cp/ΔM2-2中其表示包含突变cp和ΔM2-2的RSV D46)除了存在以使名称更容易阅读之外没有任何意义,特别是当出现在文本中时。因此,RSV D46/cp/ΔM2-2与RSVD46cpΔM2-2相同。此外,RSV D46/cp/ΔM2-2也与RSVD46cpΔM2-2或RSVD46cpΔM2-2等相同。此外,病毒名称通常以RSV开头,如RSV D46/cp/ΔM2-2。

[0232] 4.如前所述,“ΔM2-2”突变是指241-核苷酸缺失以及三点突变,如图1所示。使M2-2 ORF沉默的其他突变由不同的名称指定,例如ΔM2-2-AclI和ΔM2-2-HindIII如图10所示。本公开中病毒名称中“ΔM2-2”的存在表明存在“ΔM2-2”突变。

[0233] 5.体内病毒复制的量级用作病毒减毒的指示:具体地,体内复制减少用作减毒增加的指示,反之亦然。这反映了一般观察到增加的RSV复制与wtRSV感染(例如,El Saleeby,et al.2011.J Infect Dis 204:996-1002;DeVincenzo,et al.2010.Am J Respir Crit Care Med 182:1305-1314)和临床研究中减毒的RSV候选(例如Karron,et al.1997.J Infect Dis 176:1428-1436;Karron,et al.2005.J Infect Dis 191:1093-1104)二者的疾病增加相关。这些术语用于描述目的,而不是作为限制性定义。

[0234] 实施例1

[0235] 本实施例说明了单独和与另外的突变组合的在M2-2ORF中带有缺失的新型RSV变体(ΔM2-2)的设计和构建。

[0236] 临床前构建和评估了代表性病毒。该小组的一种代表性病毒和来自另一来源的第二种M2-2ORF突变病毒在血清阴性婴儿和幼儿的1期临床研究中进行了评估,其构成了主要的儿科RSV疫苗靶组。本实施例提供了新疫苗株以及最相关人群中代表性实例的临床基准。

[0237] RSV rA2-K5病毒.先前构建了称为RSV rA2-K5的RSV毒株(来自亲本wt D46cDNA衍生的病毒),其中M2-2ORF的表达通过三种类型的突变的组合沉默:(i)在M2-2ORF的中途引入移码(frame shift),(ii)将M2-2ORF的三个潜在的ATG翻译起始密码子(参见图1A,RSV基因组图和重叠的M2-1和M2-2-ORF的图示)变为ACG密码子,和(iii)在M2-1ORF结束后不久将终止密码子引入M2-2序列的所有三个登记(register)中(Bermingham and Collins.1999.Proc Natl Acad Sci USA 96:11259-11264)。评估该rA2-K5病毒(本公开中未示出)在血清阴性黑猩猩的呼吸道中的复制,显示其在上呼吸道中被限制至少2800倍并且在下呼吸道中未被检测到(代表减少至少55,000倍)(Teng,et al.2000.J Virol 74:9317-9321)。

[0238] RSV D46/ΔM2-2和RSV LID/ΔM2-2的生成.构建了另外的重组病毒,其中大部分M2-2ORF被缺失。修饰wt D46cDNA,使得M2-2ORF的三个潜在翻译ATG起始密码子中的每一个都变为ACG,并且缺失核苷酸8188-8428(共缺失241个核苷酸),去除大部分M2-2ORF(图1)。因此,在所有已知的潜在ATG翻译起始位点突变并且大部分ORF缺失的情况下,完整M2-2蛋白的表达应该是不可能的,并且应该很少或不表达任何截短的M2-2片段。得到的RSV D46/ΔM2-2病毒的基因图谱如图2所示。

[0239] 构建额外的ΔM2-2突变体,其具有一系列减毒表型。因为原型RSV rA2-K5病毒在黑猩猩中高度减毒,如上所述(Teng,et al.2000.J Virol 74:9317-9321),其中未表达M2-2的病毒可能过度减毒。另一方面,它也可能是减毒不足的,特别是在血清阴性的婴儿和幼儿中。因此,构建了另外的病毒变体以鉴定具有增加和减少的复制的衍生物。

[0240] 没有建立的方法来增加RSV株的复制,特别是ΔM2-2突变体。之前有报道称将G和F基因从基因顺序中的第6和第7基因(这是在SH基因被缺失的病毒中完成的,因此G和F是第6和第7基因而不是在其第7和第8的天然位置)分别移动成为第1和第2基因,导致体外复制增加～10倍,尽管小鼠中(Krempl,et al.2002.J Virol 76:11931-11942)或AGM的复制没有统计学上显著的增加。一个限制是用于评估RSV复制和减毒的已建立的临床前测定(例如,在细胞系、啮齿动物和除黑猩猩之外的非人类灵长类动物中的复制)可能是相对半允许的和不敏感的,使得难以在统计学上证明复制效率的显著变化,因此复制的任何变化似乎都值得注意,即使不是在每个测定中都检测到。因此,试图修饰ΔM2-2/ΔSH病毒以将G和F基因移动到启动子近端位置。(ΔSH缺失已被包括在野生型骨架的初始研究中[Krempl,et al.2002.J Virol 76:11931-11942]以避免在细菌中质粒扩增期间该序列的不稳定性并被认为是偶然的,并且ΔSH缺失也与ΔM2-2-骨架一起使用)。评估了几种排列,如其中将G和F基因分别放置在第一和第二基因,或分别作为第二和第一基因。然而,这些修饰使病毒复制减少了100至1000倍,表明这些特定变化在感染性病毒中不能很好地耐受。可能是已知与其基因向启动子近端位置移动相关(Krempl,et al.2002.J Virol 76:11931-11942)的G和F的表达增加结合上与ΔM2-2突变相关的蛋白质的增加不被RSV耐受,至少在这种ΔM2-2/ΔSH骨架中是这样。

[0241] 另外,已知基因组长度的变化会影响复制效率。具体地,已经显示增加副粘病毒基因组的长度可降低其复制效率。例如,以不扰乱基因表达的方式将RSV基因组的长度增加140或160个核苷酸导致对小鼠中的复制的5至25倍限制(Bukreyev,Murphy,Collins.2000.J Virol 74:11017-11026)。在另一项使用相关病毒即人副流感病毒3型(PIV3)的研究中,在仓鼠中通过添加额外基因或通过非翻译区域插入增加基因组长度(因此不改变基因编号)来增加基因组长度保留了体外的有效复制但减毒(Skiadopoulos,et al.2000.Virology 272:225-234)。据推测,由于复制较长的基因组的负担较大,因此发生与基因组长度增加相关的减毒。增加基因组长度降低复制效率的观察结果表明了相反的观点,即减少基因组长度可能会提高复制效率。为此,修饰RSV D46/ΔM2-2病毒以包含称为“6120”的突变,产生称为RSV LID/ΔM2-2的病毒(图2中显示的基因组图,底部图)。在本文档中,病毒名称中的“LID”表示存在6120突变。

[0242] “6120”突变(图3)涉及缺失SH基因的下游非翻译区的112个核苷酸,并在最后三个密码子和SH基因的终止密码子中引入五个翻译-沉默点突变(Bukreyev,et al.2001.J Virol 75:12128-12140)。该突变的原始设计的主要目的是稳定细菌中的反基因组cDNA,使其更容易操作和制备,事实确实如此。在wt RSV中,先前发现该突变使体外复制效率提高5倍(Bukreyev,et al.2001.J Virol 75:12128-12140),而它似乎没有增加小鼠中的复制效率。当评估RSV LID/ΔM2-2与6120突变相关的体外复制增加的可能性时,在一些实验中观察到生长效率的适度增加,但在其他实验中没有观察到。

[0243] RSV D46/ΔM2-2和RSV LID/ΔM2-2中额外突变的纳入.构建了RSV D46/ΔM2-2和

RSV LID/ΔM2-2病毒的一系列进一步衍生物,其中将一种或多种额外的突变以不同方式插入一种或两种病毒中,目的是获得进一步减毒的病毒谱。

[0244] RSV D46/ΔM2-2的衍生物的实例显示在图4中。例如,衍生的RSV D46/cp/ΔM2-2病毒(图4,顶部图)将ΔM2-2突变(图1)与"cp"突变组合,其为三种蛋白(N(V267I)、F(E218A和T523I)和L(C319Y和H1690Y))中的一组5个氨基酸取代,其一起(凭其自身)使血清阴性黑猩猩中复制减少约10倍,并减少疾病(Whitehead,et al.1998.J Virol 72:4467-4471)。来自黑猩猩的表型数据的可用性是值得注意的,因为该实验动物在其对RSV复制和疾病的允许性方面接近人类。注意D46/cp/ΔM2-2构建体在DNA水平上在D46骨架中具有单个不定核苷酸变化:具体地,存在于M ORF中的沉默核苷酸变化G3878A。

[0245] 另一种衍生物,RSV D46/ΔM2-2/1030s病毒(图4,自顶部的第二个图),包含ΔM2-2突变与遗传稳定的由1321K(AAA)/S1313(TCA)组成的1030突变("1030s")(Luongo,et al.2012.J Virol 86:10792-10804)的组合。1030s突变分别在小鼠的上呼吸道和下呼吸道中赋予RSV复制0.6和1.5的平均$\log_{10}$减少。它也已经在血清阴性黑猩猩中进行了评估,但仅与许多额外的减毒突变相结合(Luongo,et al.2012.J Virol 86:10792-10804)。

[0246] 另一种衍生物RSV D46/cp/ΔM2-2/HEK病毒(图4,底部图)将cp和ΔM2-2突变与"HEK"突变组合。HEK突变由RSV F蛋白中的两个氨基酸取代K66E和Q101P组成,其在氨基酸水平使该序列匹配称为HEK-7的相同株(A2)的早期传代(通过在人胚肾(HEK)细胞上将原始株A2临床分离株传代7次衍生)(Connors,et al.1995.Virology 208:478-484;Whitehead,et al.1998.J Virol 72:4467-4471),且被认为最近似原始株A2临床分离株(并且可能与其相同)(Liang,et al.2014.J Virol 88:4237-4250;Liang,et al.2015.J Virol 89:9499-9510)。先前已经表明,HEK突变稳定了F蛋白三聚体并且赋予了一种被认为类似于原始临床分离株的低融合表型(Liang,et al.2014.J Virol 88:4237-4250;Liang,et al.2015.J Virol 89:9499-9510)。除了可能在原始株A2临床分离株中发现之外,在GenBank中存在的几乎所有RSV亚组A的临床分离株中都发现了HEK分配(Liang,et al.2015.J Virol 89:9499-9510)。因此,HEK突变可以提供更真实和免疫原性形式的RSV F蛋白,可能富集高免疫原性的融合前构象(McLellan et al.,Science 2013 340(6136):1113-7;Science 2013 342(6158):592-8.)。因此,HEK突变本身不是必然与减毒相关联,而是提供F蛋白的一种形式,其更准确地反映原始株A2临床分离株以及其他RSV株的临床分离株。

[0247] RSV LID/ΔM2-2的衍生物的实例显示在图5中。一种衍生物RSV LID/cp/ΔM2-2病毒(图5,顶部图)组合了ΔM2-2和cp突变。另一种是RSV LID/ΔM2-2/1030s病毒(图5,自顶部的第二个图),其组合ΔM2-2和1030s突变。另一种是RSVΔSH/ΔM2-2病毒(图5,自顶部的第三个图),其组合具有SH基因的缺失的ΔM2-2突变(SH缺失的构建的详细信息参见图6)。先前显示SH基因的缺失导致血清阴性黑猩猩中RSV复制减少40倍,并且疾病减少(Whitehead,et al.1999.J Virol 73:3438-3442)。另一种衍生物RSV cp/ΔSH/ΔM2-2病毒(图5,下图)将ΔM2-2和cp突变与SH基因的缺失组合。注意,缺失整个SH基因的病毒不称为"LID",因为SH基因的缺失除去了6120突变。

[0248] 使用标准方法通过反向遗传学容易地回收图2、4和5中的所有突变体。然而,与基于先前工作的预期相反(例如,Bukreyev et al.,J Virol 1997 71:8973-8982;Whitehead

et al.J Virol 73:3438-3442 1999)，在ΔM2-2突变的上下文中包含ΔSH突变的病毒复制效率比其他ΔM2-2突变体低约10倍。这一发现说明了在实际制作和评估病毒时，意外但重要的影响如何产生。

[0249] 关于图4和图5中提到的减毒突变，先前对cp、ΔSH、1030(1030s的亲本)和ΔM2-2突变的黑猩猩的研究表明其逐渐增加的减毒顺序为：cp≈ΔSH<1030s<ΔM2-2(Whitehead,et al.1999.J Virol 73:3438-3442;Whitehead,et al.1999.J Virol 73:871-877;Teng,et al.2000.J Virol 74:9317-9321)。因此，cp、ΔSH和1030s突变，当单独组合或与ΔM2-2突变组合时，提供一系列逐渐增加水平的加合的减毒。这些可以在相关疫苗靶标群体(血清阴性婴儿和幼儿)的临床研究中评估。

[0250] 实施例2

[0251] 本实施例描述了LID和D46ΔM2-2病毒的临床前评估。

[0252] 评估本公开的代表性病毒在BALB/c小鼠的呼吸道中的复制，即：RSV D46wt、RSV LID/ΔM2-2、RSV ΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s和RSV cp/ΔSH/ΔM2-2(图7)。用5.8$\log_{10}$的所示病毒鼻内接种动物，并在接种后第4天和第5天处死动物，收集鼻甲和肺，均质化，并通过RT-qPCR评估，其提供比测定感染性颗粒更灵敏的检测，且因此对于这种半允许的实验动物是有用的。这表明所有含有减毒突变的病毒都比wt D46病毒更受限制。因此，各种减毒突变的进一步添加进一步减毒，尽管这种半允许啮齿动物模型中的复制水平如此受到限制以至于详细的比较是不可行的(图7)。

[0253] 研究了相同的四种含ΔM2-2的病毒在AGM呼吸道中的复制，即：RSV LID/ΔM2-2、RSV ΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s和RSV cp/ΔSH/ΔM2-2(图8A和8B，表1-3)。AGM是一种比啮齿动物更为真实的RSV复制模型，因为它与RSV的天然人类宿主具有更接近的系统发育和解剖学相关性。此外，与恒河猴和食蟹猴相比，AGM支持稍微更高水平的RSV复制，因此似乎是最合适的可用猴模型。然而，AGM对RSV复制仅是半允许的，并且AGM中RSV复制的水平显著低于黑猩猩或人类。通过组合的IN和IT途径接种四个一组的AGM，其中两个位点(IN和IT)的每个6$\log_{10}$PFU/ml。第1-10天和第12天每天采集NP拭子，并在第2、4、6、8、10和12天进行气管灌洗(表1和2)。这表明包含一种或多种额外减毒突变的所有三种病毒比RSV LID/ΔM2-2更加减毒。特别是，RSVΔM2-2/1030s病毒似乎是减毒最多的。所有这三种病毒均诱导RSV中和血清抗体的滴度比RSV LID/ΔM2-2少约为2倍(RSVΔSH/ΔM2-2和RSV cpΔSH/ΔM2-2)或4倍(RSV LID/ΔM2-2/Δ1030s)，与一般预期一致，即复制水平降低和导致的抗原负荷降低可能与免疫原性降低有关，因此应注意鉴定耐受性良好但具有足够免疫原性的RSV疫苗候选物。

[0254] 表1.来自以RSV LID/ΔM2-2、RSV ΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s或RSV cp/ΔSH/ΔM2-2接种的AGM的鼻咽拭子样本的病毒滴度[a]

[0255]

RSV候选疫苗	AGM ID	在所示天数的NP病毒滴度($\log_{10}$PFU/mL)[b]											脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		1	2	3	4	5	6	7	8	9	10	12			

[0256]

RSV LID/ΔM2-2	7806	-	1.4	1.7	2.7	2.6	4.0	3.9	1.4	-	2.7	-	9	4.0	21.4
	7705	-	-	-	2.7	2.3	3.6	2.4	1.2	-	-	-	5	3.6	14.3
	7747	-	-	1.3	0.7	-	1.5	1.3	-	-	-	-	5	1.5	7.2
	7674	-	0.7	-	-	-	2.3	1.8	1.5	-	-	-	7	2.3	8.8
	平均值:												**6.5**	**2.9**	**12.9**
RSV ΔSH/ΔM2-2	7811	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7796	-	-	-	-	1.4	-	-	-	-	-	-	1	1.4	4.9
	7789	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7808	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	平均值:												**0.3**	**0.6**	**4.1**
RSV LID/ΔM2-2/1030s	8033	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7720	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7844	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7847	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	平均值:												**0**	**0.35**	**3.9**
RSV cp/ΔSH/ΔM2-2	8008	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7741	-	-	-	1.2	1.0	-	0.7	-	1.2	-	-	6	1.2	6.6
	7765	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7637	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	平均值:												**1.5**	**0.6**	**4.5**

[0257] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.0$\log_{10}$PFU指定病毒(总剂量:每只动物6.3$\log_{10}$PFU)。

[0258] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在37℃对Vero细胞进行病毒滴定。检测下限为0.7$\log_{10}$PFU/mL。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0259] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0260] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.35的值。

[0261] 表2.来自以RSV LID/ΔM2-2、RSV ΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s或RSV cp/ΔSH/ΔM2-2接种的AGM的气管灌洗样本的病毒滴度[a]

[0262]

RSV 候选疫苗	AGM ID	在所示天数的气管灌洗病毒滴度($\log_{10}$ PFU/mL)[b]						脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		2	4	6	8	10	12			
RSV	7806	2.5	3.4	4.6	-	-	-	7	4.6	12.6

[0263]

LID/ΔM2-2	7705	1.6	-	3.3	1.5	-	-	9	3.3	8.5
	7747	1.8	1.0	6.0	2.3	-	-	9	6.0	12.5
	7674	-	1.3	2.7	2.3	1.0	-	9	2.7	8.7
	平均值:							**9.0**	**4.2**	**10.6**
RSV ΔSH/ ΔM2-2	7811	-	-	-	-	1.3	-	3	1.3	4.8
	7796	-	-	-	-	-	-	0	0.7	4.2
	7789	-	-	-	-	-	-	0	0.7	4.2
	7808	-	1.6	-	-	-	-	3	1.6	5.1
	平均值:							**1.5**	**1.1**	**4.5**
RSV LID/ΔM2-2/1030s	8033	-	-	-	-	-	-	0	0.7	4.2
	7720	-	-	-	-	-	-	0	0.7	4.2
	7844	-	-	-	-	-	-	0	0.7	4.2
	7847	-	-	-	-	-	-	0	0.7	4.2
	平均值:							**0**	**0.7**	**4.2**
RSV cp/ΔSH/ΔM2-2	8008	-	-	-	-	-	-	0	0.7	4.2
	7741	-	-	-	-	-	-	0	0.7	4.2
	7765	-	-	-	-	-	-	0	0.7	4.2
	7637	1.0	-	-	-	-	-	3	1.0	4.5
	平均值:							**0.8**	**0.8**	**4.3**

[0264] [a]通过组合的鼻内和气管内途径接种AGM,每个部位用1mL接种物中6.0log$_{10}$PFU的所示病毒(总剂量:每只动物6.3log$_{10}$PFU)。AGM研究得到NIAID,NIH动物护理和使用委员会的批准。

[0265] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在37℃对Vero细胞进行病毒滴定。检测下限为1.0log$_{10}$PFU/mL灌洗液。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0266] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0267] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.7的值。

[0268] 表3.来自以RSV LID/ΔM2-2、RSV ΔSH/ΔM2-2、RSV LID/ΔM2-2/1030s或RSV cp/ΔSH/ΔM2-2接种的AGM的中和抗体滴度[a]

[0269]

RSV 候选疫苗	**AGM ID**	**在所示天数的中和抗体滴度(PRNT$_{60}$, 倒数 log$_2$)[b]**		
		0	**21**	**28**
RSV LID/ΔM2-2	7806	<3.3	7.2	7.2
	7705	<3.3	8.8	8.2
	7747	<3.3	8.3	8.4
	7674	<3.3	6.7	6.2
	平均值:	**<3.3**	**7.8**	**7.5**
RSV ΔSH/	7811	<3.3	6.9	5.9
	7796	<3.3	7.2	7.1

[0270]

ΔM2-2	7789	<3.3	6.5	5.8
	7808	<3.3	7.1	7.2
	平均值:	**<3.3**	**6.9**	**6.5**
RSV LID/ ΔM2-2/1030s	8033	<3.3	5.4	6.6
	7720	<3.3	<3.3	<3.3
	7844	<3.3	<3.3	4.3
	7847	<3.3	6.8	6.8
	平均值:	<3.3	4.7	5.2
RSV cp/ΔSH/ΔM2-2	8008	<3.3	6.3	6.8
	7741	<3.3	6.4	5.8
	7765	<3.3	6.0	5.9
	7637	<3.3	6.3	6.3
	平均值:	**<3.3**	**6.3**	**6.2**

[0271] [a]每个部位用1mL接种物中的6.0log$_{10}$指定病毒i.n.和i.t.接种AGM(总剂量＝6.3log$_{10}$PFU每动物)。

[0272] [b]在p.i.第0、21和28天获得血清。在60％噬斑减少中和测定中测定中和抗体滴度。检测下限为3.3(1:10)。

[0273] 在AGM中进行另一个实验以比较RSV LID/ΔM2-2与以下三种病毒:D46/ΔM2-2、RSV D46/cp/ΔM2-2、D46/cp/ΔM2-2/HEK(表4-6)。这表明RSV LID/ΔM2-2病毒在上(表4)和下(表5)呼吸道中比RSV D46/ΔM2-2实质上更有效地复制。重要的是,由于这些病毒之间的唯一差异是RSV LID/ΔM2-2中存在的6120突变,这表明6120突变赋予灵长类动物宿主增加的复制。因此,它提供了逐步降低病毒限制和减毒水平的手段。因此,LID和D46骨架在复制效率方面提供了实质性差异,使得在任一骨架中包含额外的突变可以提供一系列减毒表型。具有额外突变的RSV D46病毒,即RSV D46/cp/ΔM2-2/HEK和RSV D46/cp/ΔM2-2,具有显著降低的复制,表明减毒增加。所有病毒均诱导RSV中和血清抗体的实质滴度(表6)。RSV LID/ΔM2-2诱导最高滴度;RSV D46/ΔM2-2和RSV D46/cp/ΔM2-2诱导的滴度降低不到2倍,且RSV D46/cp/ΔM2-2/HEK诱导的滴度几乎低6倍。这表明包含指定不同程度减毒的突变产生了一系列减毒表型。它还提供了进一步的指示,即复制减少可导致免疫原性降低。

[0274] 表4.来自以D46/cp/ΔM2-2/HEK、D46/cp/ΔM2-2、D46/ΔM2-2或RSV LID/ΔM2-2接种的AGM的鼻咽拭子样本的病毒滴度[a]

[0275]

RSV 候选疫苗	AGM ID	在所示天数的 NP 病毒滴度(log$_{10}$ PFU/mL)[b]											脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		1	2	3	4	5	6	7	8	9	10	12			
D46/cp/	8401	-	-	-	-	0.7	-	-	-	-	-	-	1	0.7	4.2

[0276]

ΔM2-2/HEK	8195	-	-	-	-	-	-	-	2.0	-	0.7	-	3	2.0	5.8
	7867	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8392	-	-	-	0.7	1.0	0.7	-	-	-	-	-	3	1.0	5.2
												平均值:	**1.8**	**1.0**	**4.8**
D46/cp/ ΔM2-2	57413	-	-	-	-	-	-	-	0.7	-	-	-	1	0.7	4.2
	8054	-	-	-	-	1.2	-	-	-	-	-	-	1	1.2	4.7
	8172	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8445	-	-	-	-	-	-	-	0.7	-	-	-	1	0.7	4.2
												平均值:	**0.8**	**0.7**	**4.2**
D46/ΔM2-2	8279	-	-	-	-	-	-	1.2	1.2	-	-	-	2	1.2	5.5
	32956	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8246	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7856	-	-	-	-	-	-	1.9	-	-	-	-	1	1.9	5.4
												平均值:	**0.8**	**1.0**	**4.7**
RSV LID/ ΔM2-2	62403	-	1.2	1.9	3.6	3.6	4.2	3.1	1.7	-	-	-	7	4.2	20.7
	8258	-	1.7	3.0	3.2	2.5	1.5	2.7	2.3	1.4	-	-	8	3.2	19.4
	8232	-	2.2	3.0	3.8	3.1	1.5	2.8	2.4	1.7	-	-	8	3.8	21.7
	582126	0.7	2.0	3.0	3.7	3.8	1.6	2.5	2.1	1.0	-	-	9	3.8	22.4
												平均值:	**8**	**3.7**	**21.0**

[0277] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.7log$_{10}$PFU指定病毒(总剂量:每只动物7.0log$_{10}$PFU)。AGM研究得到NIAID,NIH动物护理和使用委员会的批准。

[0278] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在32℃对Vero细胞进行病毒滴定。检测下限为0.7log$_{10}$PFU/mL。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0279] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0280] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.35的值。

[0281] 表5.来自以D46/cp/ΔM2-2/HEK、D46/cp/ΔM2-2、D46/ΔM2-2或RSV LID/ΔM2-2接种的AGM的气管灌洗样本的病毒滴度[a]

[0282]

RSV 候选疫苗	AGM ID	在所示天数的气管灌洗病毒滴度(log_{10} PFU/mL)[b]						脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		2	4	6	8	10	12			
D46/cp/ ΔM2-2/HEK	8401	1.5	-	-	-	-	-	3	1.5	5.0
	8195	1.3	-	-	1.7	-	-	9	1.7	5.8
	7867	-	-	1.0	1.0	-	-	5	1.0	4.8
	8392	1.5	-	1.0	1.3	-	-	9	1.5	5.6
							平均值:	**6.5**	**1.4**	**5.3**
D46/cp/ ΔM2-2	57413	1.0	-	-	-	-	-	3	1.0	4.5
	8054	-	-	1.0	-	-	-	3	1.0	4.5
	8172	1.6	-	-	-	-	-	3	1.6	5.1
	8445	-	1.6	2.2	-	-	-	5	2.2	6.6
							平均值:	**3.5**	**1.5**	**5.4**
D46/ΔM2-2	8279	-	-	-	-	-	-	0	0.7	4.2
	32956	1.7	1.8	-	-	-	-	5	1.8	6.3
	8246	1.0	-	1.6	-	-	-	7	1.6	5.4
	7856	-	-	-	-	1.0	-	3	1.0	4.5
							平均值:	**3.8**	**1.3**	**5.1**
RSV LID/ ΔM2-2	62403	1.0	3.5	3.9	1.0	-	-	7	3.9	10.5
	8258	1.0	1.7	1.0	2.9	1.8	-	9	2.9	8.8
	8232	1.6	4.2	3.1	2.7	-	-	9	4.2	12.9
	582126	1.6	2.4	2.5	2.8	-	-	9	2.8	10.7
							平均值:	**8.5**	**3.5**	**10.7**

[0283] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.7log_{10}PFU指定病毒(总剂量:每只动物7.0log_{10}PFU)。

[0284] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在32℃对Vero细胞进行病毒滴定。检测下限为1.0log_{10}PFU/mL灌洗液。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0285] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0286] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.7的值。

[0287] 表6.来自以D46/cp/ΔM2-2/HEK、D46/cp/ΔM2-2、D46/ΔM2-2或RSV LID/ΔM2-2接种的AGM的中和抗体滴度[a]

[0288]

RSV 候选疫苗	AGM ID	在所示天数的中和抗体滴度($PRNT_{60}$,倒数 log_2)[b]			
		0	14	21	28
D46/cp/ ΔM2-2/HEK	8401	<3.3	<5.3	5.3	6.3
	8195	<3.3	<5.3	6.9	7.1
	7867	<3.3	<5.3	7.1	7.4
	8392	<3.3	<5.3	5.3	5.9
	平均值:	**<3.3**	**<5.3**	**6.2**	**6.7**
D46/cp/ΔM2-2	57413	<3.3	5.8	6.8	7.9
	8054	<3.3	7.3	9.9	10.6

[0289]

	8172	<3.3	<5.3	8.0	8.6
	8445	<3.3	6.0	7.7	8.0
	平均值:	**<3.3**	**6.1**	**8.1**	**8.8**
D46/ΔM2-2	8279	<3.3	<5.3	8.3	7.9
	32956	<3.3	6.1	8.6	8.1
	8246	<3.3	5.8	8.4	8.6
	7856	<3.3	5.6	8.2	9.1
	平均值:	<3.3	5.7	8.4	8.4
RSV LID/ΔM2-2	62403	<3.3	5.9	7.8	8.7
	8258	<3.3	<5.3	7.6	8.8
	8232	<3.3	7.8	8.7	9.0
	582126	<3.3	8.2	9.4	10.2
	平均值:	**<3.3**	**6.8**	**8.4**	**9.2**

[0290] [a]每个部位用1mL接种物中的6.7$\log_{10}$指定病毒i.n.和i.t.接种AGM(总剂量＝7.0$\log_{10}$PFU每动物)。

[0291] [b]在p.i.第0、21和28天获得血清。在60％噬斑减少中和测定中测定中和抗体滴度。检测下限为3.3(1:10)。

[0292] 实施例3

[0293] 本实施例描述了RSV MEDI/ΔM2-2病毒的临床评估。

[0294] 先前描述了另一种具有修饰的M2-2的RSV突变体,命名为RSV MEDI/ΔM2-2(Jin,et al.2000.J Virol 74:74-82)。通过在反基因组cDNA中的核苷酸位置8197-8201和8431-8436处引入HindIII位点,然后进行HindIII限制性消化和连接以从M2-2ORF中缺失介入的234个核苷酸来制备RSV MEDI/ΔM2-2病毒(Jin,et al.2000.J Virol 74:74-82)。因此,RSV MEDI/ΔM2-2病毒不含有如本文所述的“ΔM2-2”突变(参见,例如,图1)。该病毒不是来自D46(其由Collins及其同事(Collins et al.Proc Natl Acad Sci USA 1995 92:11563-11567)的RSV A2株的制备物开发);而是源自RSV A2株的不同制备物(下面的实施例5描述了这些骨架之间的差异)。生产了作为活减毒鼻内疫苗适合于人体评估的RSV MEDI/ΔM2-2的临床试验材料(CTM)。确定了RSV MEDI/ΔM2-2 CTM的核苷酸序列并发现其除在三个序列位置处的二态性(两种不同核苷酸分配的混合物)外与其原始的cDNA克隆相同:(i)NS1基因中的核苷酸285,相比cDNA中的A,在CTM中为A/G的混合物,导致相比cDNA中的S,CTM中为氨基酸分配S/G的混合物;(ii)NS2基因中的核苷酸900,相比cDNA中的C,为C/T的混合物,其对氨基酸编码没有影响;且(iii)SH基因中的核苷酸4311,相比cDNA中的T,在CTM中为T/G的混合物,导致相比cDNA中的N,CTM中为氨基酸分配N/K的混合物。通常在RNA病毒中发现多态性,并且由于CTM具有高水平的感染性(通过噬斑测定确定),在斑块表型中没有表现出二态性,并且在体外有效复制,因此认为这些可能是无关紧要的。可以进行从实验动物和临床受试者脱落的病毒的序列评估,以确定这些序列差异中的任何一个是否在体内是有利的,这将指示它们中的任何一个是否是重要的。获得来自一种临床疫苗分离株的序列,并且在所有指定位点仍存在痕量的二态性,表明这些变化都不重要。

[0295] RSV MEDI/ΔM2-2在成人、RSV血清阳性儿童和RSV血清阴性婴儿和6-24个月大的儿童中相继进行的1期临床研究中作为鼻内疫苗候选得到了评估(ClinicalTrials.gov NCT01459198;Karron,et al.2015.Science Transl Med 2015 7(312):312ra175)。成人研

究是开放标签的，血清阳性和血清阴性婴儿和儿童的研究是双盲、随机和安慰剂对照的。该研究在Johns Hopkins University Bloomberg School of Public Health(JHU)的免疫研究中心(CIR)进行。

[0296] 当在成人和RSV血清阳性儿童中进行评估时，这种实验性疫苗的感染性非常差，免疫原性非常差，并且耐受性良好，正如对RSV减毒株所预期的那样。在RSV血清反应阴性的婴儿和幼儿中，20名疫苗接种者接受单剂量5.0$\log_{10}$PFU的RSV MEDI/ΔM2-2疫苗，10名受试者接受安慰剂。疫苗接种者与安慰剂相比发热和咳嗽的发生率相似，而接种疫苗者的上呼吸道疾病发生率是安慰剂的两倍(85％对44％)，尽管这没有统计学差异。两组中经常分离出多种不定的呼吸道病毒，其可能导致大部分疾病，并且在这项特定研究中混淆了疫苗耐受性的确定。不定病毒感染和疾病的发生率可能在不同研究之间不可预测地变化，并且在这种情况下，发病率异常高并且需要进一步研究以评估RSV MEDI/ΔM2-2的耐受性。通过12/20受体中的噬斑测定和17/20受体中的RT-qPCR检测鼻洗液中疫苗病毒的脱落。脱落感染性病毒的儿童的脱落病毒平均滴度为1.5$\log_{10}$PFU/ml(图9，左侧)。这些发现提出了疫苗可能在复制中过度限制的可能性，因为研究通常针对基于噬斑测定的>90％脱落，并且感染性脱落病毒的平均滴度为约2.5$\log_{10}$PFU/ml。关于抗体应答，19/20血清阴性儿童RSV中和血清抗体滴度增加≥4倍，平均滴度为6.6$\log_2$(1:97)。这表明RSV MEDI/ΔM2-2病毒基本上是免疫原性的。然而，观察到只有12/20受试者脱落感染性病毒，加上脱落疫苗病毒的低滴度，提出了RSV MEDI/ΔM2-2病毒具有次优复制的可能性，并且在一定程度上更有效复制的M2-2突变体病毒可能更有效。这是一个相关的问题，因为RSV复制并引起疾病的呼吸道表面上皮的免疫保护是低效的，且因此希望RSV疫苗具有尽可能的免疫原性。

[0297] 实施例4

[0298] 本实施例说明了RSV LID/ΔM2-2的临床评估。

[0299] 如上所述，AGM中RSV D46/ΔM2-2和RSV LID/ΔM2-2的比较表明RSV LID/ΔM2-2中“6120”突变的存在与复制增加有关(表4和5)。进一步比较RSV LID/ΔM2-2在AGM中与RSV MEDI/ΔM2-2的CTM的复制，与wt RSV平行进行(表7-9)。对NP拭子(表7)或气管灌洗样本(表8)中感染性病毒脱落的分析表明，两种病毒比平行评估的wt RSV更加减毒。然而，在RSV LID/ΔM2-2和RSV MEDI/ΔM2-2之间，脱落没有明显差异，并且因此复制没有明显差异。所有三种病毒(RSV LID/ΔM2-2，RSV MEDI/ΔM2-2和wt RSV)诱导了相似滴度的RSV中和血清抗体(表9)。

[0300] 在临床研究中评估RSV LID/ΔM2-2病毒以确定它是否可以比RSV MEDI/ΔM2-2更有效地在人中复制并且可能更具免疫原性。制造了许多适用于人类施用的RSV LID/ΔM2-2的CTM作为实验性鼻内RSV疫苗。核苷酸序列分析显示CTM具有与其cDNA克隆相同的序列，表明在制造过程中不存在可检测的不定突变。其在Vero细胞(用于疫苗生产)中的复制效率与RSV MEDI/ΔM2-2基本相同。RSV LID/ΔM2-2CTM与wt RSV平行评估AGM中的复制和免疫原性(表10-12)。从NP拭子(表10)和气管灌洗样本(表11)滴定感染性病毒证实了RSV LID/ΔM2-2CTM的减毒表型。尽管如此，由CTM诱导的RSV中和血清抗体的滴度与wt RSV诱导的滴度几乎相同(表12)，表明该实验疫苗保留了其wt亲本的大部分免疫原性。

[0301] RSV LID/ΔM2-2CTM在RSV血清阴性婴儿和6-24个月大的儿童中进行了双盲安慰剂对照研究的评估，该研究以CIR/JHU(ClinicalTrials.gov NCT02040831)和

International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT,ClinicalTrials.gov NCT02237209)的7个临床站点进行。总共有20名受试者接受单剂量的5.0log$_{10}$PFU疫苗,9名接受安慰剂。关于疫苗接种后的呼吸道疾病,疫苗接种者和安慰剂接受者经常发生呼吸道疾病。发热、中耳炎、上呼吸道疾病、下呼吸道疾病、咳嗽或任何呼吸或发热疾病的发生率在两组之间基本相同。在疫苗接种者和安慰剂接受者中经常检测到不定病毒,包括鼻病毒、腺病毒、副流感病毒和冠状病毒。单个疫苗接种者在第9天经历了轻度下呼吸道疾病(干罗音)的短暂发作,其在第11天消退,并且与疫苗病毒的脱落以及检测鼻病毒和肠病毒作为外来物巧合。因此,这种临床疾病的因果关系仍不清楚。从19/20疫苗接种者中回收感染性脱落流感疫苗病毒,平均峰值滴度为3.4log$_{10}$PFU/ml(图9B)。

[0302] 因此,基于脱落感染性病毒的个体数量(19/20对12/20)并且基于平均峰值滴度(3.4log$_{10}$PFU/ml与1.5log$_{10}$PFU/ml相比,显著不同),RSV LID/ΔM2-2病毒在人类宿主中比RSV MEDI/ΔM2-2更具感染性。RSV LID/ΔM2-2病毒也比之前在临床研究中评估过的称为rA2cp248/404/1030ΔSH的先前主要候选(Karron,et al.2005.J Infect Dis 191:1093-1104)更有效地复制:来自该先前研究的许多样本与来自MEDI/ΔM2-2研究的样本并排分析,显示rA2cp248/404/1030ΔSH的平均峰值滴度为2.5log$_{10}$(图9A,右图)。与平行分析的RSV MEDI/ΔM2-2(1:97)和rA2cp248/404/1030ΔSH(1:34)相比,RSV LID/ΔM2-2病毒也诱导了RSV中和血清抗体更高的平均滴度(1:137)。

[0303] 上述临床研究表明RSV LID/ΔM2-2病毒比RSV MEDI/ΔM2-2在人宿主中更具感染性和更有效的复制。它也更具免疫原性。如上所述,这两种病毒之间病毒复制效率的差异尚未在细胞系或AGM中可重复地证明,并且AGM中LID/ΔM2-2比MEDI/ΔM2-2的更高免疫原性也未得到证实。因此,与临床前研究相反,RSV LID/ΔM2-2为RSV MEDI/ΔM2-2提供了更具复制能力,更具免疫原性的替代方案。

[0304] 设计并构建了具有一个或多个额外减毒突变的RSV LID/ΔM2-2的其他衍生物。这些毒株的实例包括:RSV LID/cp/ΔM2-2(参见实施例8)、RSV LID/ΔSH/ΔM2-2、RSV LID/cp/ΔSH/ΔM2-2和RSV LID/ΔM2-2/1030s。根据先前对血清阴性黑猩猩的cp、ΔSH、1030s和ΔM2-2突变的评估,预计当前毒株的逐渐增加的减毒的顺序为:RSV LID/cp/ΔM2-2≈RSV LID/ΔSH/ΔM2-2<RSV LID/cp/ΔSH/ΔM2-2<RSV LID/ΔM2-2/1030s。还提供了另外的株,例如包括实施例5-8描述的突变的株。

[0305] 表7.来自以RSV LID/ΔM2-2或wt RSV rA2接种的AGM的鼻咽拭子样品中的病毒滴度[a]

[0306]

RSV 候选疫苗	AGM ID	在所示天数的 NP 病毒滴度(log_{10} PFU/mL)[b]											脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		1	2	3	4	5	6	7	8	9	10	12			
RSV LID/ΔM2-2	7845	-	-	-	-	1.2	1.5	0.7	-	-	-	-	3	1.5	6.2
	7394	-	-	0.7	-	2.1	2.4	2.6	1.9	-	-	-	6	2.6	11.8
	7802	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7832	-	-	-	-	-	2.1	-	-	-	0.7	-	5	2.1	6.0
												平均值:	3.5	1.6	7.0
RSV MEDI ΔM2-2	7534	-	-	-	-	-	-	0.7	-	-	-	-	1	0.7	4.2
	7882	-	-	1.2	0.7	0.7	1.0	1.4	1.7	2.2	1.2	-	8	2.2	11.2
	7568	-	-	-	-	0.7	-	-	-	-	-	-	1	0.7	4.2
	7890	-	-	2.2	2.3	1.3	-	1.9	0.7	-	-	-	6	2.3	10.5
												平均值:	4.0	1.5	7.5
wt RSV rA2	7822	-	-	1.0	1.3	1.0	2.6	2.7	0.7	-	1.0	-	8	2.7	11.7
	7894	-	0.7	1.0	0.7	1.4	4.0	3.7	1.7	2.0	1.5	1.0	11	4.0	18.1
	7622	-	-	2.0	1.4	2.5	2.3	-	1.9	1.3	-	-	7	2.5	13.2
	7831	-	-	-	1.0	-	-	-	-	2.1	-	-	6	2.1	6.3
												平均值:	8.0	2.9	12.3

[0307] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.0log_{10}PFU指定病毒(总剂量:每只动物6.3log_{10}PFU)。AGM研究得到NIAID,NIH动物护理和使用委员会的批准。

[0308] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在37℃对Vero细胞进行病毒滴定。检测下限为0.7log_{10}PFU/mL。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0309] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0310] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.35的值。

[0311] 表8.来自以RSV LID/ΔM2-2或wt RSV rA2接种的AGM的气管灌洗样本的病毒滴度[a]

[0312]

RSV 候选疫苗	AGM ID	在所示天数的气管灌洗病毒滴度 (log_{10} PFU/mL)[b]						脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		2	4	6	8	10	12			
RSV LID/ΔM2-2	7845	1.0	1.9	2.2	-	1.3	-	11	2.2	7.7
	7394	1.6	2.5	2.6	-	-	-	7	2.6	9.0
	7802	2.0	1.5	2.3	-	-	-	7	2.3	7.9
	7832	1.0	2.8	4.1	3.3	2.6	-	11	4.1	14.6
	平均值:							**9.0**	**2.8**	**9.8**
RSV MEDI ΔM2-2	7534	1.3	2.1	2.8	2.1	-	-	9	2.8	9.7
	7882	2.4	1.5	2.9	2.3	-	-	9	2.9	10.5
	7568	-	2.0	2.7	1.6	-	-	7	2.7	8.4
	7890	2.4	2.7	2.0	1.9	1.3	-	11	2.7	10.9
	平均值:							**9.0**	**2.8**	**9.9**
wt RSV rA2	7822	2.5	2.5	4.7	2.6	1.3	-	11	4.7	14.2
	7894	3.3	2.9	4.0	3.5	2.0	-	11	4.0	16.4
	7622	2.3	2.8	4.3	2.0	1.0	1.0	13	4.3	13.5
	7831	2.0	3.8	4.3	4.2	2.5	-	11	4.3	17.4
	平均值:							**11.5**	**4.3**	**15.4**

[0313] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.0log_{10}PFU指定病毒(总剂量:每只动物6.3log_{10}PFU)。

[0314] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在37℃对Vero细胞进行病毒滴定。检测下限为1.0log_{10}PFU/mL灌洗液。没有可检测病毒的样品表示为"-"。每只动物的峰值滴度都标有下划线。

[0315] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0316] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.7的值。

[0317] 表9.来自以RSV LID/ΔM2-2或WT RSV rA2接种的AGM的中和抗体滴度[a]

[0318]

RSV 候选疫苗	AGM ID	在所示天数的中和抗体滴度($PRNT_{60}$, 倒数 log_2)[b]		
		0	21	28
RSV LID ΔM2-2	7845	<3.3	3.3	6.7
	7394	<3.3	5.8	6.1
	7802	<3.3	8.9	9.7
	7832	<3.3	6.1	6.2
	平均值:	**<3.3**	**6.0**	**7.2**
RSV MEDI ΔM2-2	7534	<3.3	8.7	8.2
	7882	<3.3	6.9	9.1
	7568	<3.3	7	7.5
	7890	<3.3	7.6	8.8
	平均值:	**<3.3**	**7.6**	**8.4**

[0319]

wt RSV rA2	7822	<3.3	8	8.4
	7894	<3.3	7.8	7.7
	7622	<3.3	6.9	8
	7831	<3.3	5.7	6.1
	平均值:	**<3.3**	**7.1**	**7.6**

[0320] [a]每个部位用1mL接种物中的6.0log_{10}指定病毒i.n.和i.t.接种AGM(总剂量=6.3log_{10}PFU每动物)。

[0321] [b]在p.i.第0、21和28天获得血清。在60%噬斑减少中和测定中测定中和抗体滴度。

检测下限为3.3(1:10)。

[0322] 表10.来自以CTM RSV LID/ΔM2-2或以重组wt RSV rA2接种的AGM的鼻咽拭子样品的病毒滴度

[0323]

病毒[a]	AGM ID	在所示天数的NP病毒滴度(log_{10} PFU/mL)[b]											峰值病毒滴度	每日滴度总和[c]
		1	2	3	4	5	6	7	8	9	10	12		
RSV LID/ΔM2-2	7728	-	-	-	-	-	0.7	-	-	-	1.2	-	1.2	5.0
	7833	-	-	3.6	2.6	3.6	4.3	1.7	-	1.3	-	-	4.3	18.9
	7706	-	-	-	1.2	2.0	2.7	0.7	-	1.7	-	-	2.7	10.3
	7767	-	-	-	-	0.7	-	-	-	-	1.0	-	1.0	4.8
	平均值:												**2.3**	**9.8**
RSV rA2 wt RSV	7877	-	-	3.4	3.5	3.4	1.6	3.4	2.9	1.5	-	-	3.5	21.1
	7885	-	-	2.3	3.8	3.3	3.1	2.9	2.3	1.7	-	-	3.8	20.9
	7758	-	0.7	-	0.7	0.7	2.1	2.2	2.7	1.5	1.0	-	2.7	12.6
	7724	-	1.4	2.2	2.8	2.1	3.4	3.0	2.4	3.1	2.0	-	3.4	23.2
	平均值:												**3.4**	**19.4**

[0324] [a]每个部位用1mL接种物中的5.9log_{10}PFU指定病毒i.n.和i.t.接种了猴(总剂量=6.2log_{10}PFU/AGM)。

[0325] [b]在37℃对Vero细胞进行病毒滴定。检测下限为0.7log_{10}PFU/mL。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。结果显示,与RSV rA2相比,RSVLID ΔM2-2在AGM的URT中受到强烈限制。

[0326] [c]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.35的值。

[0327] 表11.来自以CTM RSV LID/ΔM2-2或以重组wt RSV rA2接种的AGM的气管灌洗样本的病毒滴度

[0328]

病毒测试产品[a]	AGM ID	在所示天数的TL病毒滴度(log_{10} PFU/mL)[b]						峰值病毒滴度	每日滴度总和[c]
		2	4	6	8	10	12		

[0329]

RSV LID ΔM2-2	7728	1.3	-	2.0	-	-	-	2.0	6.1
	7833	2.2	2.6	2.0	2.1	-	-	2.6	10.2
	7706	-	2.5	2.7	1.7	1.3	-	2.7	9.6
	7767	1.0	-	-	2.6	2.0	-	2.6	7.7
	平均值:							**2.5**	**8.4**
RSV rA2 wt RSV	7877	2.4	3.0	3.9	2.8	1.0	-	3.9	13.8
	7885	1.8	2.9	3.5	3.0	-	-	3.5	12.6
	7758	1.9	2.9	3.7	3.9	1.3	-	3.9	14.5
	7724	-	2.3	2.7	3.5	4.1	2.1	4.1	15.4
	平均值:							**3.8**	**14.1**

[0330] [a]每个部位用1mL接种物中的5.9log_{10}PFU指定病毒i.n.和i.t.接种了猴(总剂量=6.2log_{10}PFU/AGM)。

[0331] [b]在32℃对Vero细胞进行病毒滴定。检测下限为1.0log_{10}PFU/mL。没有可检测病毒

的样品表示为“-”。下划线的值表示每只动物的最大滴度。正如预期,高温敏感病毒RSV LID ΔM2-2在AGM的LRT中没有复制(体温:39℃)。TL,气管灌洗。

[0332] [c]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.7的值。

[0333] 表12.以CTM RSV LID/ΔM2-2或以重组wt RSV rA2接种的AGM中的血清$PRNT_{60}$抗体滴度

[0334]

病毒的[a]	AGM ID	在所示天数的 RSV 中和滴度(倒数 Log_2)		
		0	21	28
RSV LID/ΔM2-2	7728	-	8.1	10.1
	7833	-	7.2	7.4
	7706	-	5.7	6.4
	7767	-	6.4	6.3
	平均值:	-	**6.9**	**7.6**
RSV rA2 wt RSV	7877	-	8.6	8.5
	7885	-	8.2	9.1
	7758	-	7.8	7.9
	7724	-	7.5	7.8
	平均值:		**8.0**	**8.3**

[0335] [a]每个部位用1mL接种物中的5.9log_{10}PFU指定病毒i.n.和i.t.接种了猴(总剂量=6.2log_{10}PFU/AGM)。

[0336] [b]60%噬斑减少测定的检测下限为3.3(稀释度倒数的Log_2)。低于检测下限的样品记录为“-”。

[0337] 实施例5

[0338] 本实施例说明了可能影响体内复制效率的RSV LID/ΔM2-2、RSV D46/ΔM2-2和RSV MEDI/ΔM2-2的差异。

[0339] 如上所述,除了RSV LID/ΔM2-2的SH基因中的6120突变外,RSV D46/ΔM2-2和RSV LID/ΔM2-2病毒序列相同,后者从下游非翻译区移除了112个核苷酸并在SH ORF的最后三个密码子和终止密码子中生成沉默核苷酸改变(图3)。RSV LID/ΔM2-2在AGM的上(表4)和下(表5)呼吸道中比RSV D46/ΔM2-2显著更有效地复制。由于这些病毒在其他方面是相同的,这表明6120突变与灵长类动物的复制增加有关,并且该效果大到足以在AGM中明确地检测到。

[0340] 如上所述,RSV LID/ΔM2-2和RSV MEDI/ΔM2-2病毒在细胞培养物和AGM中的复制效率方面无法区分,但前者在血清阴性婴儿和儿童的复制中显著更有效且更具免疫原性。因此,这些病毒的复制效率也不同,但这仅在完全允许的人类宿主中才明显。RSV LID/ΔM2-2具有6210突变,而RSV MEDI/ΔM2-2没有。然而,在这种情况下,6120突变与半允许性AGM中的复制增加无关,但与血清阴性婴儿和儿童(允许的天然宿主)的复制增加有关。这些观察结果表明,尽管RSV LID/ΔM2-2明显具有比RSV MEDI/ΔM2-2更高的复制效率,但这可能会因LID和MEDI病毒之间的某些其他差异而略微降低。除了6120突变之外,还有两个这样的差异:

[0341] 其中一个不同之处在于,使M2-2ORF沉默的突变的细节在RSV LID/ΔM2-2和RSV

MEDI/ΔM2-2之间是不同的。在RSV LID/ΔM2-2(和RSV D46/ΔM2-2)中,缺失长度为241-nt,并在核苷酸8187之后开始,此外,所有三个ATG翻译起始密码子都变为ACG,由此任何M2-2衍生的肽应该很少或没有翻译(图1)。相反,在RSV MEDI/ΔM2-2中,缺失突变涉及从核苷酸8196开始插入外源HindIII限制性位点,涉及234nt的缺失,并且将编码代表最长形式的M2-2蛋白质N-末端的12-氨基酸肽(Jin,et al.2000.J Virol 74:74-82)。

[0342] 第二个差异是RSV MEDI/ΔM2-2和RSV LID/ΔM2-2cDNA在贯穿两个骨架散布的21个额外的核苷酸序列位置上不同(表13)。其中,6个核苷酸差异(包括RSV LID/ΔM2-2的1099位的1个核苷酸插入)是由于在构建D46cDNA克隆期间添加的限制性位点(Collins,et al.1995.Proc Natl Acad Sci USA 92:11563-11567)。这六种变化被认为是表型沉默的,因为生物wt RSV和重组wt D46RSV在黑猩猩中以相似的效率复制并引起相似水平的疾病(例如Whitehead,et al.1998.J Virol 72:4467-4471)。这些变化也存在于迄今为止在人类中评估的许多候选疫苗中。因此,这6个核苷酸及其相关的限制性位点似乎不太可能影响复制,尽管这尚未明确确定。RSVMEDIΔM2-2和RSV LID/ΔM2-2之间的剩余15个核苷酸差异是点突变,其被认为反映了从两种独立反向遗传学系统衍生的株A2的两种不同亲本生物病毒贮存物中存在不定差异。在具有不同传代史的相同RSV株的两种制剂之间发现许多核苷酸差异并不罕见。这15个核苷酸差异中的两个导致氨基酸差异,一个在NS2蛋白(K51R)中,另一个在N蛋白中(T24A)(氨基酸分配首先给出LID,然后是MEDI)。最近的一项研究表明,这两种氨基酸差异都不会影响体外复制效率(Lawlor,Schickli,and Tang.2013.J Gen Virol 94:2627-2635)。

[0343] 表13:除6120和ΔM2-2突变外RSV MEDI/ΔM2-2和RSV LID/ΔM2-2间基因组序列(正义)间的差异

[0344]

基因区域	RSV 核苷酸			氨基酸 (注解)		
	基因组核苷酸位置[1]	RSV MEDI/ΔM2-2 cDNA	RSV LID/ΔM2-2 cDNA	氨基酸位置	RSV MEDI/ΔM2-2 cDNA	RSV LID/ΔM2-2 cDNA
NS1	404	C	T	102	N	N
NS2	779	G	A	51	**R**	**K**
NS2/Nig	1099	T	C*	ncr[2]	n/a	(1-nt 插入，在 RSV LID/ΔM2-2 中生成 AflII 限制性位点)
N	1138	A	C*	ncr[2]	n/a	(在 RSV LID/ΔM2-2 中生成 NcoI 限制性位点)
N	1139	G	C*	ncr[2]	n/a	
N	1181	G	A	14	K	K
N	1209	G	A	24	**A**	**T**
N	1937	A	G	266	S	S
G/F ig	5611	A	G*	ncr[2]	n/a	(在 RSV LID/ΔM2-2 中生成 StuI 限制性位点)
G/F ig	5615	A	T*	ncr[2]	n/a	
G/F ig	5639	G	A	ncr[2]	n/a	n/a
F	6215	C	T	185	V	V
F	6221	C	T	187	V	V
F	6386	T	C	242	G	G
F	7214	C	T	518	A	A
F	7481	T	C	ncr[2]	n/a	n/a
F/M2 ig	7559	A	C*	ncr[2]	n/a	(在 RSV LID/ΔM2-2 中生成 SphI 限制性位点)

[0345]

M2	7701	G	C	32	P	P
L	10514	T	C	673	L	L
L	13633	A	C	1712	T	T
L	13900	T	C	1801	S	S

[0346] [1]相对于WT RSV株A2编号的基因组位置(Genbank登录号M74568)。所有序列都是正义的。

[0347] [2]ncr,非编码区域

[0348] [4]ig,基因间区域

[0349] *作为标记物工程化成原始LID反基因组cDNA克隆的变化(Collins et al.PNAS 92:11563-7 1995 PMID 8524804)。这些变化存在于已在人类中评估的大多数重组RSV疫苗候选物中。

[0350] 因此,提供了新的试剂和信息,表明:

[0351] 1.RSV LID/ΔM2-2在AGM中比RSV D46/ΔM2-2实质上更有效地复制。由于这些病毒仅在RSV LID/ΔM2-2中存在6120突变方面存在差异,因此推断该突变赋予灵长类中复制增加的表型,即使在半允许AGM模型中也可检测到这种差异。RSV LID/ΔM2-2和RSV D46/ΔM2-2之间的复制效率的这种实质性差异提供了两个在减毒方面显著不同的骨架。因此,可以将一组共同的减毒突变(例如,cp,ΔSH,1030s)引入每个骨架,并获得与人类基准数据(即RSV LID/ΔM2-2的临床研究)直接相关的广谱减毒表型。

[0352] 2.在AGM中,RSV LID/ΔM2-2没有比RSV MEDI/ΔM2-2更有效地复制,但是在允许

性更高的天然宿主(即血清阴性婴儿和儿童)中却更有效。这表明RSV LID/ΔM2-2相对于RSV MEDI/ΔM2-2具有复制优势,但与其同RSV D46/ΔM2-2相比优势较小。因此,对于RSV LID/ΔM2-2和RSV MEDI/ΔM2-2,人类中的复制效率的顺序是RSV LID/ΔM2-2>RSV MEDI/ΔM2-2,并且来自AGM的数据支持进一步的结论RSV D46/ΔM2-2甚至更加减毒,给出减毒的顺序:RSV LID/ΔM2-2>RSV MEDI/ΔM2-2>D46/ΔM2-2。这表明RSV MEDI/ΔM2-2与D46/LID骨架相比的一个或多个差异是其中间表型的原因。最有可能的候选者分别是NS2和N中的K51R和T24A突变,尽管上面公开的数据表明它们在表型上是沉默的(Lawlor,Schickli,and Tang.2013.J Gen Virol 94:2627-2635)。这两种氨基酸取代被认为是最可能的候选者,因为氨基酸变化更可能影响表型-通过对蛋白质结构和功能的影响-而不是顺式作用信号中不包含的沉默核苷酸信号。另一种或额外的可能性是ΔM2-2突变的构造细节的差异发挥作用。另一种可能性是19种其他翻译沉默核苷酸差异中的一种或多种发挥作用。使用选自下组的株可以分辨这些可能性。

[0353] 实施例6

[0354] 本实施例说明了具有来自RSV LID/ΔM2-2、RSV D46/ΔM2-2和RSV MEDI/ΔM2-2的特征组合的额外的ΔM2-2构建体。

[0355] 使用上述结果作为指导构建额外的基于ΔM2-2的病毒以获得包含几种ΔM2-2突变、6120突变、K51R/T24A突变中的一种以及MEDI和D46/LID骨架之间的其他偶然差异的不同组合。

[0356] 生成了额外的M2-2缺失,其基于定点诱变,其缺失了M2-2ORF的234个核苷酸(核苷酸8202-8435)并引入了T8197A和C8199G点突变,这产生了AclI位点并且在M2-2ORF中的密码子13引入了终止密码子(图10)。对RSV D46和RSV LID骨架进行了这种修饰,得到RSV D46/ΔM2-2-AclI和RSV LID/ΔM2-2-AclI(图11)。这些病毒将D46或LID骨架(即分别没有和具有6120突变,但在其他方面相同)与类似于RSV MEDI/ΔM2-2的ΔM2-2突变(ΔM2-2-AclI)组合,包括了表达代表M2-2的12个N-末端氨基酸的肽的可能性(图11)。

[0357] 通过在NS2蛋白中包含K51R突变和在N蛋白中包含T24A突变来进一步修饰RSV D46/ΔM2-2-AclI和RSV LID/ΔM2-2-AclI cDNA(图12A)。因此,这将相对于MEDI骨架的两种最显著的差异并入D46/ΔM2-2和LID/ΔM2-2骨架。

[0358] 作为进一步的实例,NS2蛋白中的K51R突变和N蛋白中的T24A突变也分别(图12B,自顶部的第一和第二构建体)和一起(第三构建体)引入D46/ΔM2-2骨架。这些突变也被分别(第四(构建下)和第五构建体)和一起(底部构建体)引入LID/ΔM2-2骨架(图12C)。

[0359] 此外,将ΔM2-2-HindIII突变(如图10所示)引入D46以产生D46/ΔM2-2-HindIII和LID/ΔM2-2-HindIII骨架(图13,自顶部的第一和第三构建体)。其他衍生物包括在NS2和N蛋白中进一步添加的K51R和T24A氨基酸取代(图13,自顶部的第二和第四构建体)。

[0360] 实施例7

[0361] 本实施例说明了对F和/或G基因进行额外修饰的额外的ΔM2-2构建体。

[0362] 通过对F和/或G基因的进一步改变修饰RSV LID/ΔM2-2(图2)。通常,这些修饰的设计主要不是为了影响减毒,而是为了影响其他参数,例如抗原表达的效率或包含来自另一种株的基因。注意,这些株使用术语“6120”而不是“LID”来指示6120突变的存在。这些构建体如下:

[0363] RSV 6120/G001BB/FBB/ΔM2-2(图14A):含有来自最近(2011年),低传代临床分离株A/Maryland/001/11的密码子优化的G基因(G001BB)。该构建体还含有密码子优化的株A2F基因(FBB)。注意,在细菌克隆过程中证明G0001序列的天然序列是不稳定的。产生G001BB的密码子优化具有赋予稳定性的作用。

[0364] RSV 6120/FBB/G001BB/ΔM2-2(图14A);包含密码子优化的A2F基因(FBB)和来自最近临床分离株(G001BB)的密码子优化的G基因,但它们在基因图谱中的顺序已经从G-F逆转为F-G,进而获得主要的RSV中和和保护性抗原F蛋白增加的表达。

[0365] RSV 6120/G001BB/F/ΔM2-2(图14A):包含G001BB和天然A2F基因。

[0366] RSV 6120/G/FBB/ΔM2-2(图14A,自顶部的第四构建体):包含天然A2G基因和密码子优化的A2F基因(FBB)。

[0367] RSV 6120/G/FBBHEK/ΔM2-2(图14B):包含天然A2G基因和密码子优化的A2F基因(FBB),其具有两种HEK突变,K66E和Q101P。

[0368] RSV 6120/G/FBBcpHEK/ΔM2-2(图14C):包含天然A2G基因和密码子优化的A2F基因(FBB)(其也具有两种HEK突变,K66E和Q101P)和包含于F基因中的两种cp突变(即E218A和T523I)。

[0369] RSV 6120/FBB/G/ΔM2-2(图14C):包含密码子优化的A2F(FBB)和天然A2G基因,但其在基团图谱中的顺序从G-F逆转为F-G。

[0370] RSV 6120/G001BB/F001BB/ΔM2-2(图14C):包含G001BB基因和F001基因,其已经密码子优化(G001BB,F001BB)。

[0371] 简而言之,使用来自称为A/Maryland/001/11的最近临床分离株(2011年从患有严重呼吸道疾病的医疗保健提供者中分离出来)中的G和/或F基因来研究这些组合是否可能产生改进的复制和/或免疫原性。它还表明,活RSV疫苗可以很容易地更新以包含来自更近期株的表面蛋白。密码子优化(BB)的使用为增加一种或两种主要保护性抗原的表达。G和F从G-F到F-G的基因顺序的变化经设计以增加抗原表达,并且在知道在ΔM2-2突变的背景下将F和G一直移动到基因图谱中的启动子-近端位置导致病毒意外地表现出体外复制水平降低的情况下进行,如实施例1中所述。使用HEK突变,使用或不使用两个F cp突变,以获得更稳定的F蛋白,其可能由于保留中和表位而具有优异的免疫原性。这是基于这样的想法,即RSV F蛋白的亚稳定性可能通过呈递变性抗原而促进免疫逃避(Sakurai,et al.1999.J Virol 73:2956-2962;Collins and Graham,2008.J Virol 82:2040-2055),因此提供更稳定的形式可能诱导性质上优越的免疫应答。

[0372] 图14A和14B中所示的每种病毒都很容易从cDNA中回收。传代P1是转染后的第一个传代,并且在没有滴定接种物(盲代)的情况下进行。将得到的图14A和14B中构建体的P1产量与含有6120突变的wt RSV(wt LID)和构建体的亲本RSV LID/ΔM2-2进行比较(图15)。这表明所有病毒的P1滴度与两种对照相比是有利的,唯一的例外是RSV 6120/G001BB/F001BB/ΔM2-2的P1滴度降低约3.0$\log_{10}$。然而,这个滴度在P2传代期间反弹到与其他构建体一致的水平(图15)。通常,这表明所有修饰都被很好地耐受,包括新基因,基因顺序的改变,密码子优化和HEK和/或cp突变的引入。

[0373] 实施例8

[0374] 本实施例说明了额外RSVΔM2-2构建体的评估。

[0375] 如上所述，发现RSV D46/cp/ΔM2-2(图4，顶部基因组)在Vero细胞中有效复制，这是疫苗生产所必需的，并且在AGM中高度减毒但具有高免疫原性(表4-6)。因此，制备疫苗种子病毒并用于生产D46/cp/ΔM2-2的临床试验材料(CTM)。如上所述，在DNA水平，该构建体在D46骨架中具有单个不定核苷酸变化：特别是G3878A，其存在于M ORF中并且在氨基酸水平上是沉默的。自动序列分析显示CTM的序列与cDNA的序列相同。对该CTM在AGM中的复制和免疫原性的分析证实它是高度减毒的(表14和15)，但具有高度免疫原性(表16)。在CIR/JHU(ClinicalTrials.gov识别号NCT02601612)中进行的12至59个月大的15位RSV血清阴性儿童(10名疫苗接种者，5名安慰剂接受者)中的双盲安慰剂对照研究中评估了该候选疫苗。在10^6PFU剂量的鼻内给药后，疫苗脱落是不可检测的，并且D46/cp/ΔM2-2在血清阳性儿童中具有很差的免疫原性。这表明疫苗受到高度限制和减毒，预测它对血清阴性婴儿和儿童的评估是安全和适当的。目前正在对RSV血清阴性6-24个月大的婴儿和儿童进行评估。这将提供关于有希望的候选疫苗的信息，表明它是否适合扩展研究。该信息还将为临床前和临床研究提供进一步的基准。

[0376] 此外，构建了该病毒的LID对应物LID/cp/ΔM2-2(图5，顶部基因组)。发现该病毒在Vero细胞中有效复制，并且该病毒在AGM中的复制和免疫原性分析表明它高度减毒(表17和18)，但具有高免疫原性(表19)。这表明，在血清阴性婴儿和儿童(图9B)中未完全减毒的LID/ΔM2-2中添加cp突变以产生LID/cp/ΔM2-2，导致AGM中的减毒增加(即，将表1和2、4和5、7和8，以及10和11的LID/ΔM2-2数据与表17和18的LID/cp/ΔM2-2数据进行比较)。这表明LID/cp/ΔM2-2在血清阴性人中具有增加的减毒，尽管需要临床评估来确认这一点，以确定增加减毒的幅度，并确认安全性。

[0377] 然后使用反基因组cDNA制备LID/cp/ΔM2-2的临床试验材料，其序列显示在SEQ ID NO:17中。临床试验材料的序列(LIDcpΔM2-2,Lot RSV#009B)通过共有序列分析证实，除了在核苷酸位置9,972处的C-至-T点突变外，与重组病毒来源的cDNA相匹配(注意所有序列均以正义或反基因组义(antigenomic sense)报告)。该突变在氨基酸水平上是沉默的，并且也存在于用于产生LIDcpΔM2-2,Lot RSV#009B的种子病毒中。与大多数RNA病毒一样，由于RNA依赖性RNA聚合酶的高错误率，在RSV传代过程中会出现不定突变。当这些变化不涉及已知的顺式作用信号或改变氨基酸编码时，并且如果它们不能可测量地影响病毒的体外复制和斑块大小，则认为它们在生物学上是无关紧要的。LIDcpΔM2-2临床试验材料中的沉默C9972T点突变可能是无关紧要的，但将被监测。

[0378] 在双盲安慰剂对照临床试验中，LID/cp/ΔM2-2疫苗病毒正在6-24个月大的血清阴性儿童中进行评估。至少有5名受试者接种了疫苗，在疫苗病毒预计会脱落期间没有反应原性证据，这表明这种疫苗耐受性良好。

[0379] 如已经指出的，制备了非临床实验批次的LID/ΔM2-2/1030s病毒(图5，、自顶部的第二个基因组)，并且发现其在Vero细胞中有效复制。它在AGM中进行评估并显示高度减毒(表1和2)，并且具有高免疫原性(表3)。

[0380] 使用SEQ ID NO:16中所示的反基因组cDNA制备用于LID/ΔM2-2/1030s的CTM制备物，并且自动序列分析显示临床试验材料(CTM)的序列与cDNA的相同。在双盲安慰剂对照试验中，该疫苗在6-24个月大的血清阴性儿童中进行了评估。共招募了33名受试者，预期接种者：安慰剂比例为2:1。来自30名参与者的鼻洗液通过噬斑测定(病毒培养)以及通过定量

RT-PCR(qPCR)评估疫苗病毒LID/ΔM2-2/1030s的脱落,作为减毒的量度。这表明17名受试者具有明显的疫苗病毒脱落(预计总共20名受试者接受疫苗)。通过噬斑测定,LID/ΔM2-2/1030s试验中的15/30受试者是阳性的,并且所有这些中的15个加上另外两个受试者根据qPCR是阳性的,这是更灵敏的测定。预计在疫苗施用后14-18天内脱落病毒的受试者将被发现是疫苗接种者,因此这些数据可用作疫苗病毒脱落的推定评估并因此用作减毒的推定评估。相比之下,6-24个月大的血清阴性儿童的可比群组中的RSV LID/ΔM2-2的类似脱落分析,ClinicalTrials.gov NCT02040831,通过噬斑测定和qRT-PCR发现20个疫苗接种者中的19个中的病毒脱落。在LID/ΔM2-2/1030s试验中,推定平均峰值滴度为:根据PCR为5.1log_{10}拷贝/ml,根据培养为2.9log10PFU/ml,而对于LID/ΔM2-2试验,平均峰值滴度根据PCR为5.9log_{10}拷贝/ml,根据培养为3.4log_{10}PFU/ml。因此,基于感染率和脱落病毒的滴度,LID/ΔM2-2/1030s病毒似乎比LID/ΔM2-2病毒更加减毒。对于LID/ΔM2-2/1030s病毒,三个最高个体峰值滴度分别为4.7、4.5和4.1log_{10}PFU/ml,而相比之下LID/ΔM2-2分别为5.4、5.3和5.1log_{10}PFU/ml。此外,对于LID/ΔM2-2/1030s病毒,6名受试者仅在1天内脱落感染性病毒,而相比之下LID/ΔM2-2病毒则为2名。因此,通过这些措施中的每一种,将1030s突变插入LID/ΔM2-2中,提供了作为疫苗靶标的血清阴性儿童中病毒脱落的可测量的,一致的减少。

[0381] 评估RSV LID/ΔM2-2/1030s病毒的温度敏感表型,因为1030s突变是温度敏感性突变(表20)。该分析表明,RSV LID/ΔM2-2/1030s的关闭温度(T_{SH})为40℃,小菌斑温度(T_{SP})为38℃,而野生型RSV、LID/ΔM2-2、MEDI/ΔM2-2,LID/cp/ΔM2-2和D46/cp/ΔM2-2的T_{SH}和T_{SP}>40℃。因此,RSV LID/ΔM2-2/1030s,但不是这些其他野生型和基于ΔM2-2的病毒,具有温度敏感性表型。包括两种其他已知的温度敏感病毒RSVΔNS2/Δ1313/I1314L和RSVcps2作为阳性对照,并证实该测定是准确的。因此,将1030s突变引入RSV LID/ΔM2-2赋予了温度敏感表型。这是重要的,因为与较冷的上呼吸道相比,温度敏感表型被认为优先限制在较温暖的下呼吸道中的复制,因此赋予针对反应原性的额外安全性。即使T_{SH}和/或T_{SP}高于生理温度,也认为是这种情况。

[0382] 因此,这提供了具有逐渐减少的复制的减毒病毒谱:LID/ΔM2-2>LID/cp/ΔM2-2>LID/ΔM2-2/1030s,其具有不同的减毒和免疫原性平衡。

[0383] 表14:来自以D46/cp/ΔM2-2接种的AGM的鼻咽拭子样本的病毒滴度

[0384]

RSV 候选疫苗[a]	AGM ID	在所示天数的NP病毒滴度(log_{10} PFU/mL)[b]											峰值病毒滴度
		1	2	3	4	5	6	7	8	9	10	14	
D46/cp/ΔM2-2	8573	-	-	0.7	-	-	-	-	-	0.7	-	-	0.7
	N1327	-	-	0.7	-	-	-	1.0	-	-	-	-	1.0
	8555	-	-	-	-	-	-	-	-	-	-	-	0.35
	8577	-	-	-	-	-	-	0.7	-	-	-	-	0.7
	平均值:	-	-	**0.5**	-	-	-	**0.6**	-	**0.4**	-	-	**0.7**
L-15	8551	-	-	-	-	-	-	-	-	-	-	-	-
	8417	-	-	-	-	-	-	-	-	-	-	-	-
	8489	-	-	-	-	-	-	-	-	-	-	-	-
	8565	-	-	-	-	-	-	-	-	-	-	-	-
	平均值	-	-	-	-	-	-	-	-	-	-	-	-

[0385] [a]在每个位点使用在1mL接种物中6log$_{10}$PFU的所示病毒i.n.和i.t.接种猴(总剂量=6.3log$_{10}$PFU/AGM)。

[0386] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在32℃对Vero细胞进行病毒滴定。检测下限为0.7log$_{10}$PFU/mL。没有可检测病毒的样品表示为"-"。对于没有可检测病毒的样品,使用0.35的值。结果表明,D46/c/pΔM2-2在AGM的URT中受到严格限制。

[0387] 表15.来自以D46/cp/ΔM2-2接种的AGM的气管灌洗样品的病毒滴度

[0388]

RSV候选疫苗[a]	AGM ID	在所示天数的TL病毒滴度(log$_{10}$ PFU/mL)[b]						峰值病毒滴度
		2	4	6	8	10	14	
D46/cp/ΔM2-2	8573	1.0	-	1.9	1.3	-	-	1.9
	N1327	-	1.0	1.8	1.0	-	-	1.8
	8555	-	-	-	-	-	-	0.7
	8577	-	-	-	-	-	-	0.7
	平均值:	**0.8**	**0.8**	**1.3**	**0.9**	**-**	**-**	**1.9**
L-15	8551	-	-	-	-	-	-	-
	8417	-	-	-	-	-	-	-
	8489	-	-	-	-	-	-	-
	8565	-	-	-	-	-	-	-

[0389]

	平均值:	-	-	-	-	-	-	-

[0390] [a]在每个位点使用在1mL接种物中6log$_{10}$PFU的所示病毒i.n.和i.t.接种猴(总剂量=6.3log$_{10}$PFU/AGM)。

[0391] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在32℃对Vero细胞进行病毒滴定。检测下限为1.0log$_{10}$PFU/mL。没有可检测病毒的样品表示为"-"。对于没有可检测病毒的样品,使用0.7的值。D46/cp/ΔM2-2在AGM的LRT中受到严格限制。

[0392] 表16.来自以D46/cp/ΔM2-2接种的AGM的血清PRNT$_{60}$滴度.

[0393]

RSV候选疫苗	AGM ID	在所示天数的中和抗体滴度(PRNT$_{60}$,倒数log$_2$[b]		
		0	21	29
D46/cp/ΔM2-2[a]	8573	-	8.4	8.4
	N1327	-	8.4	9.1
	8555	-	6.6	6.1
	8577	-	7.2	6.9
	平均值:	-	**7.7**	**7.6**
L-15	8551	-	-	-
	8417	-	-	-
	8489	-	-	-
	8565	-	-	-
	平均值:	-	-	-

[0394] [a]在每个位点使用在1mL接种物中6.0log$_{10}$PFU的所示病毒i.n.和i.t.接种AGM(总剂量=6.3log$_{10}$PFU每只动物)。

[0395] [b]在p.i.第0、21天和第29天,获得血清。在60%噬斑减少中和测定中测定中和抗体滴度。检测下限为3.3(1:10)。

[0396] 表17:来自以LID/cp/ΔM2-2接种的AGM的鼻咽拭子样品的病毒滴度

[0397]

RSV 候选疫苗[a]	AGM ID	在所示天数的 NP 病毒滴度(log_{10} PFU/mL)[b]											峰值病毒滴度
		1	2	3	4	5	6	7	8	9	10	12	
LID/cp/ΔM2-2	8120	-	-	-	-	-	-	-	-	-	-	-	0.35
	8528	-	-	-	-	-	-	-	-	-	-	-	0.35
	8336	-	-	-	0.7	-	-	-	-	-	-	-	0.7
	平均值:	-	-	-	**0.5**	-	-	-	-	-	-	-	**0.5**

[0398] [a]在每个位点使用在1mL接种物中6log_{10}PFU的所示病毒i.n.和i.t.接种猴(总剂量=6.3log_{10}PFU/AGM)。对于没有可检测病毒的样品,使用0.35的值。

[0399] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在32℃对Vero细胞进行病毒滴定。检测下限为0.7log_{10}PFU/mL。没有可检测病毒的样品表示为“-”。对于没有可检测病毒的样品,使用0.35的值。结果表明,LID/cp/ΔM2-2在AGM的URT中受到强烈限制。

[0400] 表18:来自以LID/cp/ΔM2-2接种的AGM的气管灌洗样品的病毒滴度

[0401]

RSV 候选疫苗[a]	AGM ID	在所示天数的 TL 病毒滴度(log_{10} PFU/mL)[b]						峰值病毒滴度
		2	4	6	8	10	12	
LID/cp/ΔM2-2	8120	2.1	-	-	-	-	-	2.1
	8528	1.0	-	-	-	-	-	1.0
	8336	-	1.0	-	-	-	-	1.0
	平均值:	**1.3**	**0.8**	-	-	-	-	**1.4**

[0402] [a]通过鼻内和气管内组合途径接种AGM,每个部位用1mL接种物中的6.0log_{10}PFU指定病毒(总剂量:每只动物6.3log_{10}PFU)。

[0403] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在32℃对Vero细胞进行病毒滴定。检测下限为1.0log_{10}PFU/mL灌洗液。没有可检测病毒的样品表示为“-”。对于没有可检测病毒的样品,使用0.7的值。LID/cp/ΔM2-2在AGM的LRT中受到严格限制。

[0404] 表19:来自以LID/cp/ΔM2-2接种的AGM的血清$PRNT_{60}$滴度.

[0405]

RSV 候选疫苗	AGM ID	在所示天数的中和抗体滴度($PRNT_{60}$,倒数 log_2)[b]		
		0	21	29
LID/cp/ΔM2-2[a]	8120	-	10.0	10.5
	8528	-	10.1	9.8
	8336	-	8.1	7.7
	平均值:	-	**9.4**	**9.3**

[0406] [a]每个部位用1mL接种物中的6.0log_{10}指定病毒i.n.和i.t.接种AGM(总剂量=6.3log_{10}PFU每只动物)。

[0407] [b]在p.i.第0、21和29天获得血清。在60%噬斑减少中和测定中测定中和抗体滴度。检测下限为3.3(1:10)

[0408] 表20:RSV LID/ΔM2-2/1030s和相关病毒的温度敏感性

[0409]

病毒	在所示温度(°C)的病毒滴度(log_{10} PFU/mL)[a]								
	32	35	36	37	38	39	40	T_{SH}[b]	T_{SP}[c]
RSV A2	7.3	7.2	7.2	7.2	7.3	7.2	7.0	>40	>40
D46 6120	7.7	7.7	7.6	7.6	7.6	7.4	7.4	>40	>40

[0410]

	LID ΔM2-2	5.9	5.9	5.8	5.7	5.7	5.6	5.4	> 40	> 40
	Medi ΔM2-2	7.0	7.0	6.9	7.0	7.0	6.9	6.8	> 40	> 40
	LID cp ΔM2-2	4.5	4.5	4.4	4.2	4.1	3.9	3.5	> 40	> 40
	LID ΔM2-2 1030s	7.1	7.0	7.0	7.0	6.8*	6.1	**1.7**	40	38
	D46 cp ΔM2-2	6.2	6.2	6.1	6.0	5.9	5.7	5.5	> 40	> 40
	RSV ΔNS2 Δ1313 I1314L[XX]	7.1	6.9	6.8*	6.4	*6.4*[d]	**≤ 2**	< 2	39	36
	RSV cps2[XX]	6.4	5.8*	*4.7*[d]	**≤ 2**	< 2	< 2	< 2	37	35

[0411] [a]通过在指定温度对Vero细胞的噬斑测定来评估每种病毒的ts表型。对于具有ts表型的病毒,标记关闭温度(T_{SH})的滴度(粗体,下划线)。有关T_{SH}的定义,请参见脚注b。

[0412] [b]T_{SH}(粗体,下划线)定义为最低限制温度,在该温度下相比32℃的降低与wt RSV在这两温度下观察到的相比是100倍或更多。ts表型定义为T_{SH}为40℃或更低。

[0413] [c]T_{SP},小斑温度定义为观察到小斑表型的最低限制温度。在最低限制温度的滴度标有星号。

[0414] [d]斜体:微斑块温度定义为观察到小斑表型的最低限制温度。微斑表型的最低限制温度下的滴度用星号标记。

[0415] [XX]对照ts病毒

[0416] 实施例9

[0417] 本实施例描述了RSV D46/276/ΔM2-2-AclI的构建,以及其在非洲绿猴中与RSV D46/NS2/N/ΔM2-2-HindIII和选择的对照病毒的比较。

[0418] 构建额外的M2-2突变病毒以代表来自D46/ΔM2-2和MEDI/ΔM2-2骨架的特征的进一步组合,产生称为RSV D46/276/ΔM2-2-AclI的病毒,其在本文中也称为“RSV 276”或“276”。

[0419] RSV 276的结构总结于图16和表21中,并且在SEQ ID NO:19中提供。与D46(即,完整的野生型反基因组cDNA,SEQ ID NO:1)相比,RSV 276的差异在于共21个核苷酸的区别(包括1099位的单个nt的缺失)加核苷酸8202-8435(含端点)的缺失,产生234个核苷酸的缺失。核苷酸变化去除了在其原始构建期间有意插入D46的四个非天然限制性位点(AflII、NcoI、StuI和SphI)(Collins,et al.1995 Proc Natl Acad Sci USA 92:11563-11567),并且另外插入跨越M2-2缺失的AclI位点(因此,ΔM2-2-AclI缺失与图10中描述的相同)。限制性位点的这些变化涉及8个核苷酸。其他13个变化中的大多数将来自RSV MEDI/ΔM2-2的所选分配引入到了新RSV 276病毒的D46衍生骨架中。

[0420] 表21:wt RSV D46(cDNA,SEQ ID NO:1)和RSV 276(cDNA和CTM Lot RSV#014A,SEQ ID NO:19)的基因组序列的比较(正义)

[0421]

基因区域	RSV 核苷酸(cDNA)				编码的氨基酸残基		
	基因组 nt 位置[1]	SEQ ID NO: 1 位置	WT D46 RSV	RSV 276	氨基酸位置[1]	WT D46 RSV	RSV 276
NS1	404	404	T	C	102	N	N
NS2	779	779	A	G	51	K	R[3]
NS2/Nig[4]	1099	1099	C*	-	ncr[2]	n/a	n/a
N	1138	1139	C*	A	ncr[2]	n/a	n/a
N	1139	1140	C*	G	ncr[2]	n/a	n/a
N	1181	1182	A	G	14	K	K
N	1209	1210	A	G	24	T	A[3]
G/Fig[4]	5611	5612	G*	A	ncr[2]	n/a	n/a
G/Fig[4]	5615	5616	T*	A	ncr[2]	n/a	n/a
G/Fig[4]	5639	5640	A	G	ncr[2]	n/a	n/a
F	6215	6216	T	C	185	V	V
F	6221	6222	T	C	187	V	V
F	6386	6387	C	T	242	G	G
F	7214	7215	T	C	518	A	A
F	7481	7482	C	T	ncr[2]	n/a	n/a
F/M2ig[4]	7559	7560	C*	A	ncr[2]	n/a	n/a
M2-1	7701	7702	C	G	32	P	P
M2-2	8197	8198	T	A**	13	Y	终止密码子
M2-2	8199	8200	C	G**	15	C	非翻译的
M2-2 deletion				8202-8435 (234 nt)			aa 13-90[3]: M2-2 缺失
L	10514	10515	C	T	673	L	L
L	13633	13634	C	A	1712	T	T

[0422] [1]在表21中,核苷酸和氨基酸序列的编号相对生物wt RSV株A2(GenBank登录号M74568),其是RSV株A2的第一个完整序列。该基因组的长度为15,222nt。因此,病毒中的缺失或插入不会改变剩余核苷酸(或氨基酸)的序列编号。除非另有说明,否则核苷酸和氨基酸序列分配相对RSV D46 WT(SEQ ID NO:1)。D46是株A2的第二种重组衍生形式,其由于在1099位(如所示)的单核苷酸插入而在核苷酸长度上不同,导致基因组核苷酸长度为15,223。在RSV 276中移除了这个插入,并且该位置的分配变为T。

[0423] [2]ncr,非编码区。

[0424] [3]RSV 276中与RSV D46不同的氨基酸以灰色阴影显示。

[0425] [4]ig,基因间区域

[0426] *工程改造进D46以产生四个限制性位点标记的变化(Collins et al PNAS 92:11563-7 1995 PMID 8524804)。这些在RSV 276中被移除。

[0427] **在RSV 276中产生AclI位点的核苷酸变化。

[0428] 使用D46反基因组cDNA(SEQ ID NO:1)与合成的cDNA片段组合构建276病毒。具体地,合成cDNA,其跨越质粒载体中前导区上游的独特NotI位点至D46中N基因中2129-2134位的独特AvrII位点。合成第二个cDNA,其跨越D46中的独特XhoI位点(4481-4486位)至独特的BamHI位点(8499-8505位)。后一片段还含有ΔM2-2-AclI突变,除了所需的AclI位点是

HindIII(通过两个核苷酸的顺序倒置而不同的限制性位点,未显示)。通过常规分子克隆技术将这两个片段取代入D46,从而实现图16和表21中所示的大多数所需的核苷酸变化。然后,进行三个定点诱变步骤:将HindIII位点改变为所需的AclI位点(涉及改变两个相邻的核苷酸),并制备L中的C10514T和C13633A取代。这产生了RSV 276的反基因组cDNA(SEQ ID NO:19)。

[0429] RSV 276病毒很容易作为实验批次回收,并证实在Vero细胞中有效复制。此外,许多RSV 276病毒临床试验材料在适合人类使用的条件下回收和制造,以准备临床试验。它的序列被证实没有不定突变。

[0430] 此外,为病毒D46/NS2/N/ΔM2-2-HindIII制备了许多临床试验材料(参见图13,自顶部的第二种病毒)。D46/NS2/N/ΔM2-2-HindIII反基因组cDNA的序列显示在SEQ ID NO:18中。D46/NS2/N/ΔM2-2-HindIII(Lot RSV#011B)的临床试验材料的序列与重组病毒所衍生的cDNA质粒相匹配,除了三种多态性:(1)G2485A(～20-40%A);密码子:GAT到AAT;氨基酸:P ORF中的D47N;(2)在SH基因的3'非编码区中的多胸苷段(nt 4537-39)中的单核苷酸胸苷插入(+1nt;存在于约30%的亚群中);(3)L基因末端信号的聚腺苷段(nt 14,830-35)中的两个核苷酸的腺苷插入(在约30%的群体中+1A,在约70%的群体中+2A)。这些多态性在生物学上被认为是无关紧要的。

[0431] 在一系列研究中,测试了实验批次的RSV 276和三个不同批次的RSV RSV D46/NS2/N/ΔM2-2-HindIII在非洲绿猴中的复制和免疫原性。由于时间和动物可用性的限制,每个制备物被单独评估。结果在表22、23和24中与从表1中得到的两个比较物(LID/ΔM2-2和LID/ΔM2-2/1030s)的数据平行比较。病毒复制通过定量病毒脱落来评估,其通过NP拭子(表22)和气管灌洗(表23)取样,通过噬斑测定法定量。这表明,在上呼吸道(通过NP拭子)中,在5.5-7.3天的时间内三批D46/NS2/N/ΔM2-2-HindIII中的两个(研究2和3)可检测地脱落(平均峰值滴度为1.1-1.6log10PFU/ml),而第三批(研究1)的脱落是最小的。在下呼吸道(气管灌洗)中,三个批次的结果非常相似,在7.8-9.2天内具有中等水平的脱落(2.2-2.6log10PFU/ml)。相比之下,在上呼吸道中RSV 276的脱落与D46/NS2/N/ΔM2-2-HindIII研究2和3的脱落非常相似,并且与下呼吸道脱落中的所有三项研究非常相似。相比之下,LID/ΔM2-2在两个解剖学区室中的脱落显著更多,而LID/ΔM2-2/1030s的脱落显著更少。在第28天这些病毒的60%PRNT滴度对于D46/NS2/N/ΔM2-2-HindIII批次的2个为8.3和8.5倒数log2,第三批次为6.3倒数log2,且RSV 276为8.5倒数log2。这些滴度通常等于或超过LID/ΔM2-2和LID/ΔM2-2/1030s所示的滴度(表24)。因此,这些病毒基于ΔM2-2骨架提供了另一种减毒表型谱。

[0432] 表22:来自以LID ΔM2-2、LID ΔM2-2 1030s、D46/NS2/N/ΔM2-2-HindIII或RSV 276接种的AGM的鼻咽拭子样本的病毒滴度[a]

[0433]

RSV 候选疫苗	AGM ID	在所示天数的 NP 病毒滴度(log_{10} PFU/mL)[b]											脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		1	2	3	4	5	6	7	8	9	10	12			
LID ΔM2-2	7806	-	1.4	1.7	2.7	2.6	4.0	3.9	1.4	-	2.7	-	9	4.0	21.4
	7705	-	-	-	2.7	2.3	3.6	2.4	1.2	-	-	-	5	3.6	14.3
	7747	-	-	1.3	0.7	-	1.5	1.3	-	-	-	-	5	1.5	7.2
	7674	-	0.7	-	-	-	2.3	1.8	1.5	-	-	-	7	2.3	8.8
												平均值:	6.5	2.9	12.9
LID ΔM2-2 1030s	8033	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7720	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7844	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	7847	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
												平均值:	0	0.35	3.9
D46/NS2/N/ ΔM2-2-*Hind* III (研究 1)	8417	0.7	-	-	-	-	-	-	-	-	-	-	1	0.7	4.2
	8489	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8515	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8574	-	-	-	-	-	-	-	1.2	-	-	-	8	1.2	4.7
												平均值:	2.3	0.7	4.2
D46/NS2/N/ ΔM2-2-*Hind* III (研究 2)	N1330	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	N1326	-	-	-	1.0	0.7	-	1.8	-	1.0	-	-	6	1.8	6.9
	8566	-	-	-	1.0	0.7	0.7	-	0.7	0.7	-	-	6	1.0	5.9
	8551	-	-	-	1.0	0.7	1.0	-	-	-	-	-	3	1.0	5.5
												平均值:	3.8	1.1	5.5

[0434]

D46/NS2/N/ ΔM2-2-*Hind* III (研究 3)	9041	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8938	-	-	-	-	1.3	1.3	1.3	1.9	1.0	-	-	5	1.9	8.9
	8926	-	-	-	-	-	0.7	-	1.4	1.4	-	-	4	1.4	6.3
	8911	-	-	-	0.7	1.0	1.0	2.2	2.3	1.0	-	-	6	2.3	10.0
												平均值:	3.8	1.6	7.3
RSV 276	8918	-	-	-	-	-	-	-	-	-	-	-	0	0.35	3.9
	8902	-	1.5	2.0	2.9	2.5	3.0	3.1	2.5	1.4	1.3	-	9	3.1	21.0
	8913	-	-	-	-	-	0.7	1.4	1.0	-	-	-	3	1.4	6.0
	8952	-	-	-	-	0.7	0.7	1.5	-	-	1.2	-	6	1.5	6.5
												平均值:	4.5	1.6	9.3

[0435] [a]通过组合的鼻咽和气管内途径接种AGM,其中每个位点使用1mL接种物中10^6PFU的所示病毒(总剂量:每只动物2x10^6PFU)。AGM研究由NIAID,NIH的动物护理和使用委员会批准。显示先前对LID ΔM2-2和LID ΔM2-21030s的研究结果用于比较。

[0436] [b]将组合的NP拭子置于2mL L-15培养基中,其中含有蔗糖磷酸盐缓冲液作为稳定剂。在37℃对Vero细胞进行病毒滴定。检测下限为0.7log_{10}PFU/mL。没有可检测病毒的样品表示为“-”。每只动物的峰值滴度都标有下划线。

[0437] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0438] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.35的值。

[0439] 表23.来自以LID ΔM2-2、LID ΔM2-2 1030s、D46/NS2/N/ΔM2-2-HindIII或RSV 276接种的AGM的气管灌洗样品的病毒滴度[a]

[0440]

RSV 候选疫苗	AGM ID	在所示天数的气管灌洗病毒滴度 (log_{10} PFU/mL)[b]						脱落的持续时间[c]	峰值病毒滴度	每日滴度总和[d]
		2	4	6	8	10	12			
LID ΔM2-2	7806	2.5	3.4	4.6	-	-	-	7	4.6	12.6
	7705	1.6	-	3.3	1.5	-	-	9	3.3	8.5
	7747	1.8	1.0	6.0	2.3	-	-	9	6.0	12.5
	7674	-	1.3	2.7	2.3	1.0	-	9	2.7	8.7
							平均值:	9	4.2	10.6
LID ΔM2-2 1030s	8033	-	-	-	-	-	-	0	0.7	4.2
	7720	-	-	-	-	-	-	0	0.7	4.2
	7844	-	-	-	-	-	-	0	0.7	4.2
	7847	-	-	-	-	-	-	0	0.7	4.2
							平均值:	0	0.7	4.2
D46/NS2/N/	8417	-	2.3	2.5	1.6	1.3	-	7	2.5	9.1
	8489	1.0	2.7	3.2	3.2	-	-	9	3.2	11.5

[0441]

ΔM2-2-*Hind*III (研究 1)	8515	1.3	2.0	-	1.7	-	-	9	2.0	7.1
	8574	1.8	2.1	2.2	1.7	-	-	9	2.2	9.1
							平均值:	9	2.5	9.2
D46/NS2/N/ ΔM2-2-*Hind*III (研究 2)	N1330	0.7	1.0	0.7	0.7	-	-	3	1.0	4.5
	N1326	1.7	1.7	1.8	2.5	-	-	9	2.5	9.1
	8566	1.8	0.7	3.2	2.4	-	-	9	3.2	9.5
	8551	1.9	2.3	1.7	0.7	-	-	7	2.3	8.0
							平均值:	7	2.2	7.8
D46/NS2/N/ ΔM2-2-*Hind*III (研究 3)	9041	2.0	1.9	2.3	0.7	-	-	9	2.3	8.3
	8938	1.0	1.6	2.5	2.5	-	-	9	2.5	9.0
	8926	0.7	0.7	2.6	1.7	-	-	9	2.6	7.1
	8911	2.2	2.6	0.7	3.0	-	-	9	3.0	9.8
							平均值:	9	2.6	8.6
RSV 276	8918	0.7	1.7	2.3	1.6	1.0	-	9	2.3	8.0
	8902	2.2	1.6	2.9	2.1	0.7	-	9	2.9	10.3
	8913	0.7	0.7	3.2	1.3	0.7	-	5	3.2	7.3
	8952	1.8	2.1	1.6	1.8	0.7	-	9	2.1	8.8
							平均值:	8.0	2.6	8.6

[0442] [a]通过鼻内和气管内组合途径接种AGM,每个部位使用1mL接种物中的10^6PFU指定病毒(总剂量:每只动物2x10^6PFU)。显示先前对LID ΔM2-2和LIDΔM2-2 1030s的研究结果用于比较。

[0443] [b]在第2、4、6、8、10和12天,用3mL PBS进行气管灌洗。在37℃对Vero细胞进行病毒滴定。检测下限为1.0log_{10}PFU/mL灌洗液。没有可检测病毒的样品表示为"-"。每只动物的峰值滴度都标有下划线。

[0444] [c]检测到病毒的第一天到最后一天的天数,包括其间的阴性天数(如果有的话)。

[0445] [d]每日滴度的总和用作对脱落量级的估计(曲线下面积)。对于没有可检测病毒的样品,使用0.7的值。

[0446] 表24.以LID ΔM2-2、LID ΔM2-2 1030s、D46/NS2/N/ΔM2-2-HindIII或RSV 276接种的AGM的中和抗体滴度[a]

[0447]

RSV 候选疫苗	AGM ID	在所示天数的中和抗体滴度($PRNT_{60}$，倒数 log_2)[b]		
		0	21	28
LID ΔM2-2	7806	<3.3	7.2	7.2
	7705	<3.3	8.8	8.2
	7747	<3.3	8.3	8.4
	7674	<3.3	6.7	6.2
	平均值:	**<3.3**	**7.8**	**7.5**
LID ΔM2-2 1030s	8033	<3.3	5.4	6.6
	7720	<3.3	<3.3	<3.3
	7844	<3.3	<3.3	4.3
	7847	<3.3	6.8	6.8
	平均值:	**<3.3**	**4.7**	**5.2**

[0448]

D46/NS2/N/ ΔM2-2-*Hind*III (研究 1)	8417	<3.3	8.8	10.4
	8489	<3.3	6.6	8
	8515	<3.3	6.1	6.4
	8574	<3.3	9.4	8.2
	平均值:	**<3.3**	**7.7**	**8.3**
D46/NS2/N/ ΔM2-2-*Hind*III (研究 2)	N1330	<3.3	8.2	8.8
	N1326	<3.3	8.3	9.1
	8566	<3.3	7	7.3
	8551	<3.3	8.9	8.7
	平均值:	**<3.3**	**8.1**	**8.5**
D46/NS2/N/ ΔM2-2-*Hind*III (研究 3)	9041	<3.3	6.9	6.4
	8938	<3.3	7.1	7.2
	8926	<3.3	6.7	5.5
	8911	<3.3	7.2	5.9
	平均值:	**<3.3**	***7.0***	***6.3***
RSV 276	8918	<3.3	6.1	6.2
	8902	<3.3	8.4	8.8
	8913	<3.3	8.8	8.9
	8952	<3.3	9.7	9.9
	平均值:	**<3.3**	**8.3**	**8.5**

[0449] [a]每个部位用1mL接种物中的10^6PFU指定病毒i.n.和i.t.接种AGM(总剂量＝$10^{6.3}$PFU每只动物)。显示先前对LID ΔM2-2和LID ΔM2-2 1030s的研究结果用于比较。

[0450] [b]在p.i.第0、21和28天获得血清。在60％噬斑减少中和测定中测定中和抗体滴度。检测下限为3.3(1:10)

[0451] 显而易见的是，在不脱离所述实施方案的精神的情况下，可以改变或修改所描述的方法或组合物的精确细节。我们要求保护落在以下权利要求的范围和精神内的所有这些修改和变化。

[0001] 序列表

[0002] <110> 美利坚合众国,由健康及人类服务部部长代表

[0003] <120> 提供一系列减毒表型的在M2-2 ORF中具有突变的重组呼吸道合胞病毒株

[0004] <130> 9668-98193-02

[0005] <150> US 62/266,199

[0006] <151> 2015-12-11

[0007] <160> 19

[0008] <170> PatentIn 版本3.5

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[3230] cttagtcctt acaataggtc ctgcgaatat attcccagta tttaatgtag tacaaaatgc 14340
[3231] taaattgata ctatcaagaa ccaaaaattt catcatgcct aagaaagctg ataaagagtc 14400
[3232] tattgatgca aatattaaaa gtttgatacc ctttctttgt taccctataa caaaaaaagg 14460
[3233] aattaatact gcattgtcaa aactaaagag tgttgttagt ggagatatac tatcatattc 14520

[3234] tatagctgga cgtaatgaag ttttcagcaa taaacttata aatcataagc atatgaacat 14580

[3235] cttaaaatgg ttcaatcatg ttttaaattt cagatcaaca gaactaaact ataaccattt 14640

[3236] atatatggta gaatctacat atccttacct aagtgaattg ttaaacagct tgacaaccaa 14700

[3237] tgaacttaaa aaactgatta aaatcacagg tagtctgtta tacaactttc ataatgaata 14760

[3238] atgaataaag atcttataat aaaaattccc atagctatac actaacactg tattcaatta 14820

[3239] tagttattaa aaattaaaaa tcatataatt ttttaaataa cttttagtga actaatccta 14880

[3240] aagttatcat tttaatcttg gaggaataaa tttaaaccct aatctaattg gtttatatgt 14940

[3241] gtattaacta aattacgaga tattagtttt tgacactttt tttctcgt 14988

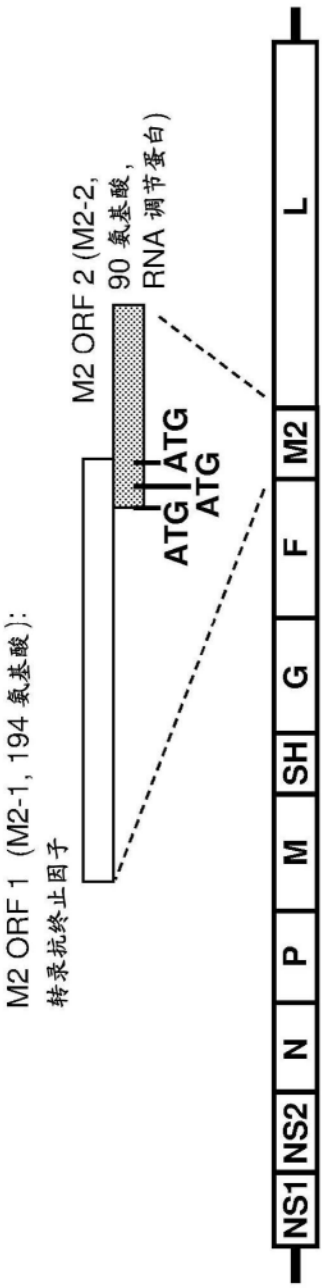
M2 ORF 1 (M2-1, 194 氨基酸):
转录抗终止因子
M2 ORF 2 (M2-2,
90 氨基酸,
RNA 调节蛋白)
ATG
ATG
ATG
NS1
NS2
N
P
M
SH
G
F
M2
L

图1A

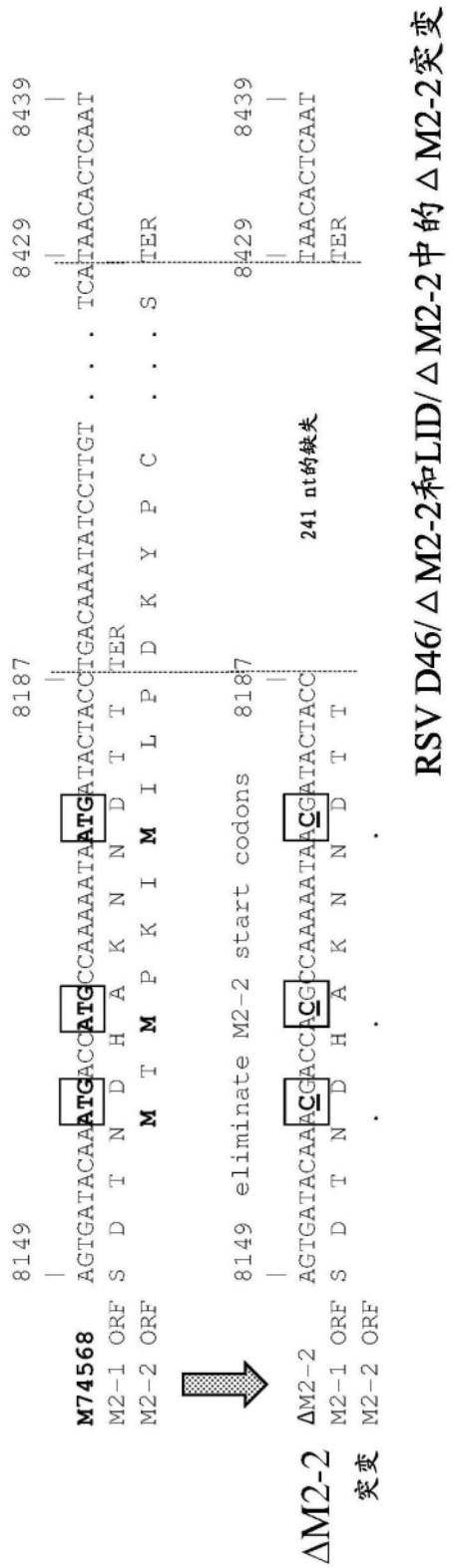
RSV D46/ΔM2-2和LID/ΔM2-2中的ΔM2-2突变
M74568
M2-1 ORF
M2-2 ORF
8149
8187
8429
8439
241 nt的缺失
8149 eliminate M2-2 start codons 8187
ΔM2-2
ΔM2-2
突变

图1B

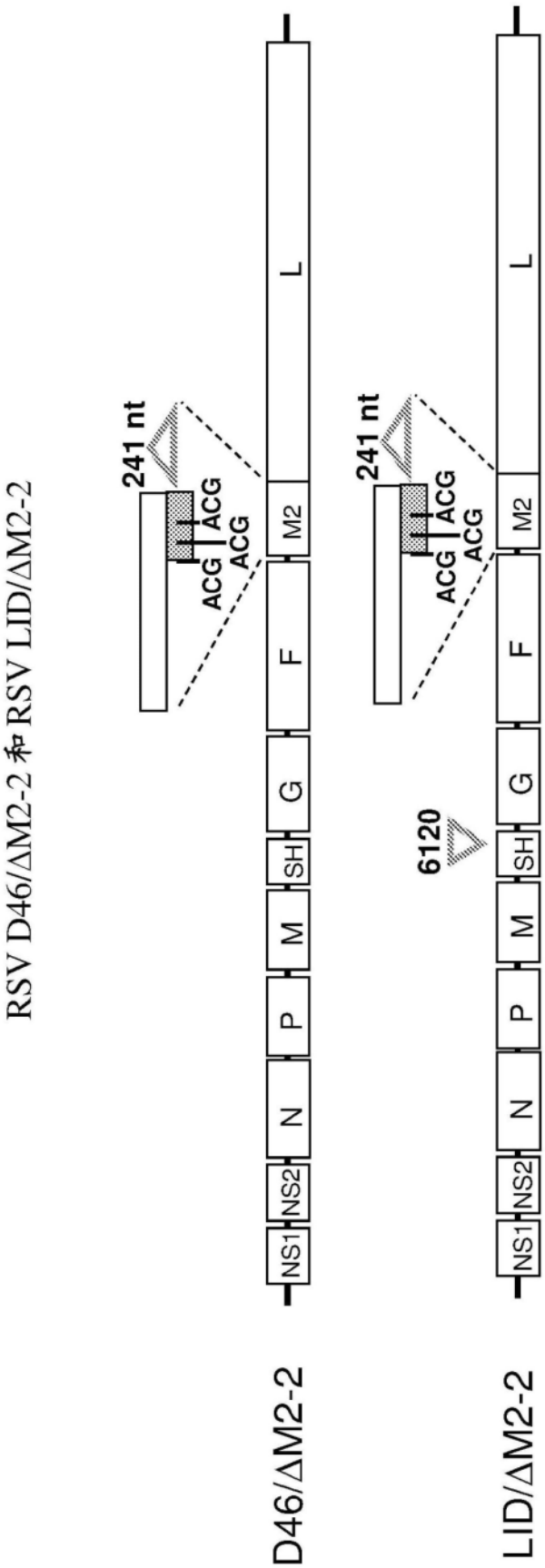
RSV D46/ΔM2-2 和 RSV LID/ΔM2-2
241 nt
ACG
ACG
NS1
NS2
N
P
M
SH
G
F
M2
L
D46/ΔM2-2
241 nt
ACG
ACG
6120
NS1
NS2
N
P
M
SH
G
F
M2
L
LID/ΔM2-2

图2

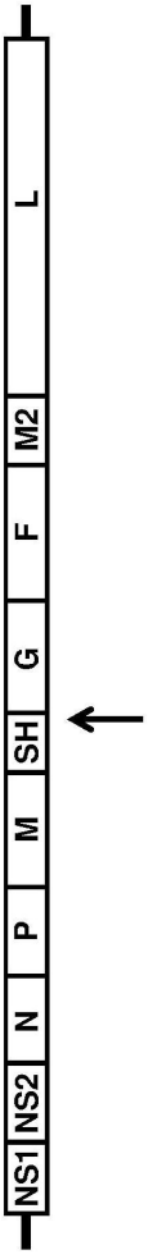

图3A

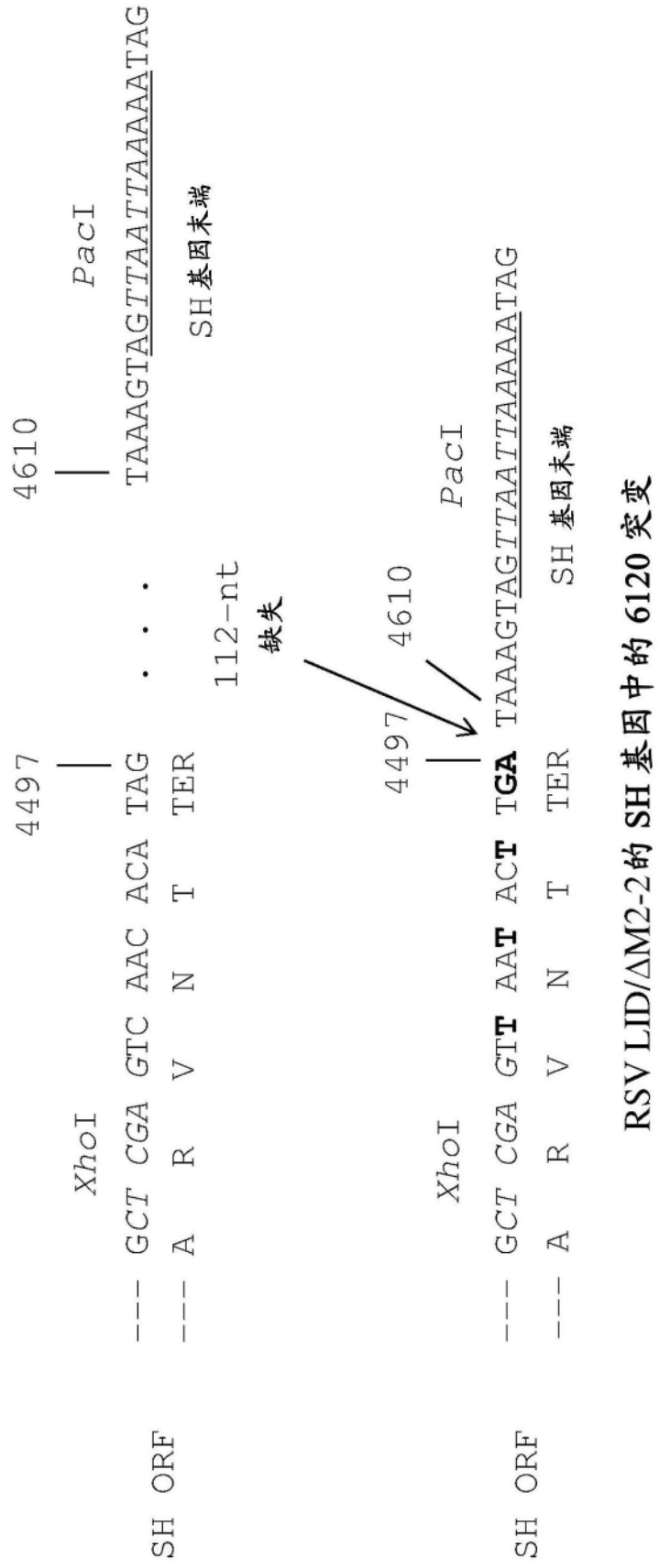
4610
PacI
TAAAGTAGTTAATTAAAAATAG
SH基因末端
4497
XhoI
--- GCT CGA GTC AAC ACA TAG . . . .
--- A R V N T TER
SH ORF
112-nt
缺失
4610
PacI
4497
XhoI
--- GCT CGA GTT AAT ACT TGA TAAAGTAGTTAATTAAAAATAG
--- A R V N T TER
SH 基因末端
SH ORF
RSV LID/ΔM2-2的 SH 基因中的 6120 突变

图3B

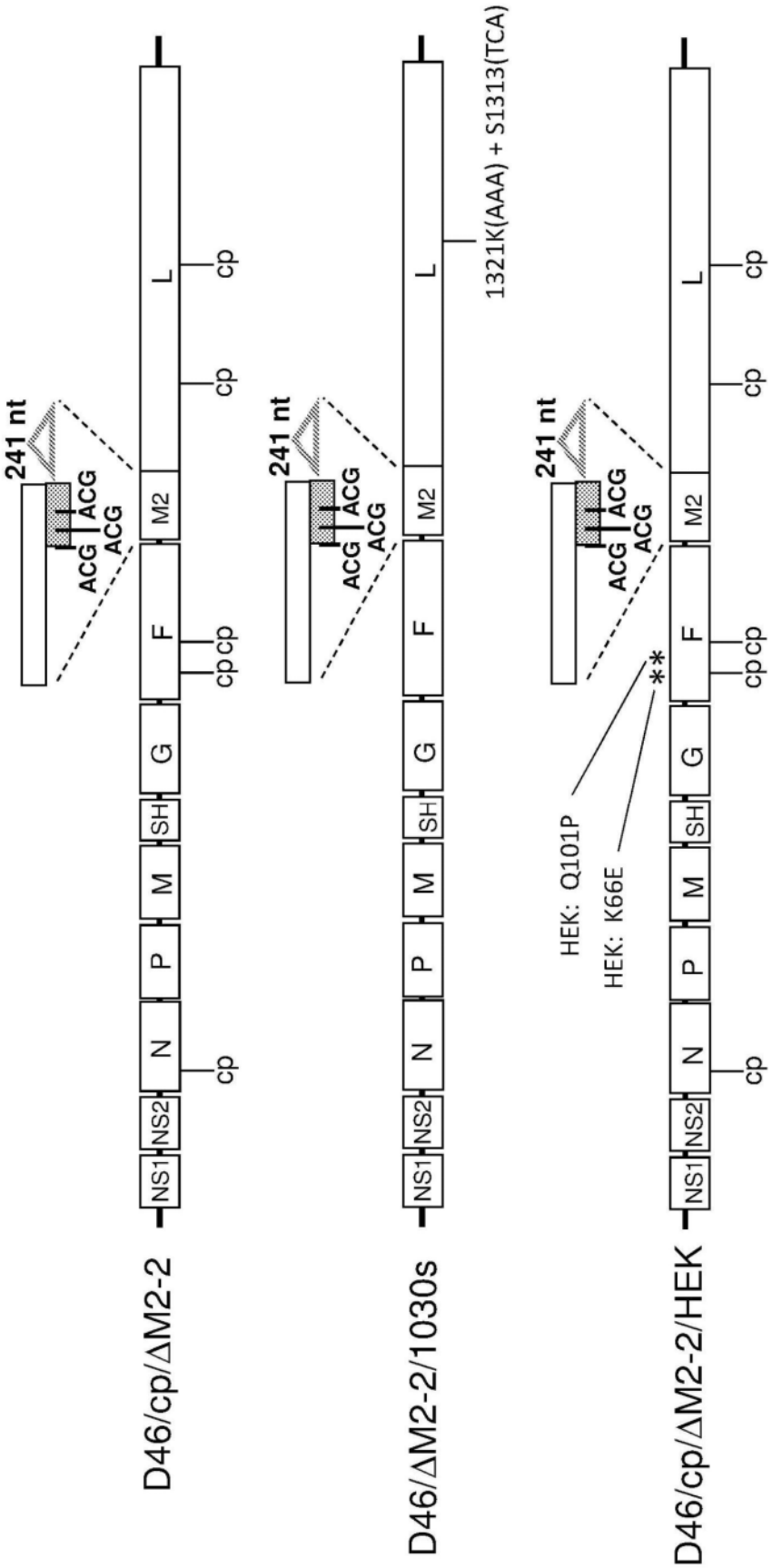
241 nt
ACG
ACG
ACG
NS1
NS2
N
P
M
SH
G
F
M2
L
cp
D46/cp/ΔM2-2
D46/ΔM2-2/1030s
1321K(AAA) + S1313(TCA)
D46/cp/ΔM2-2/HEK
HEK: Q101P
HEK: K66E
**

图4

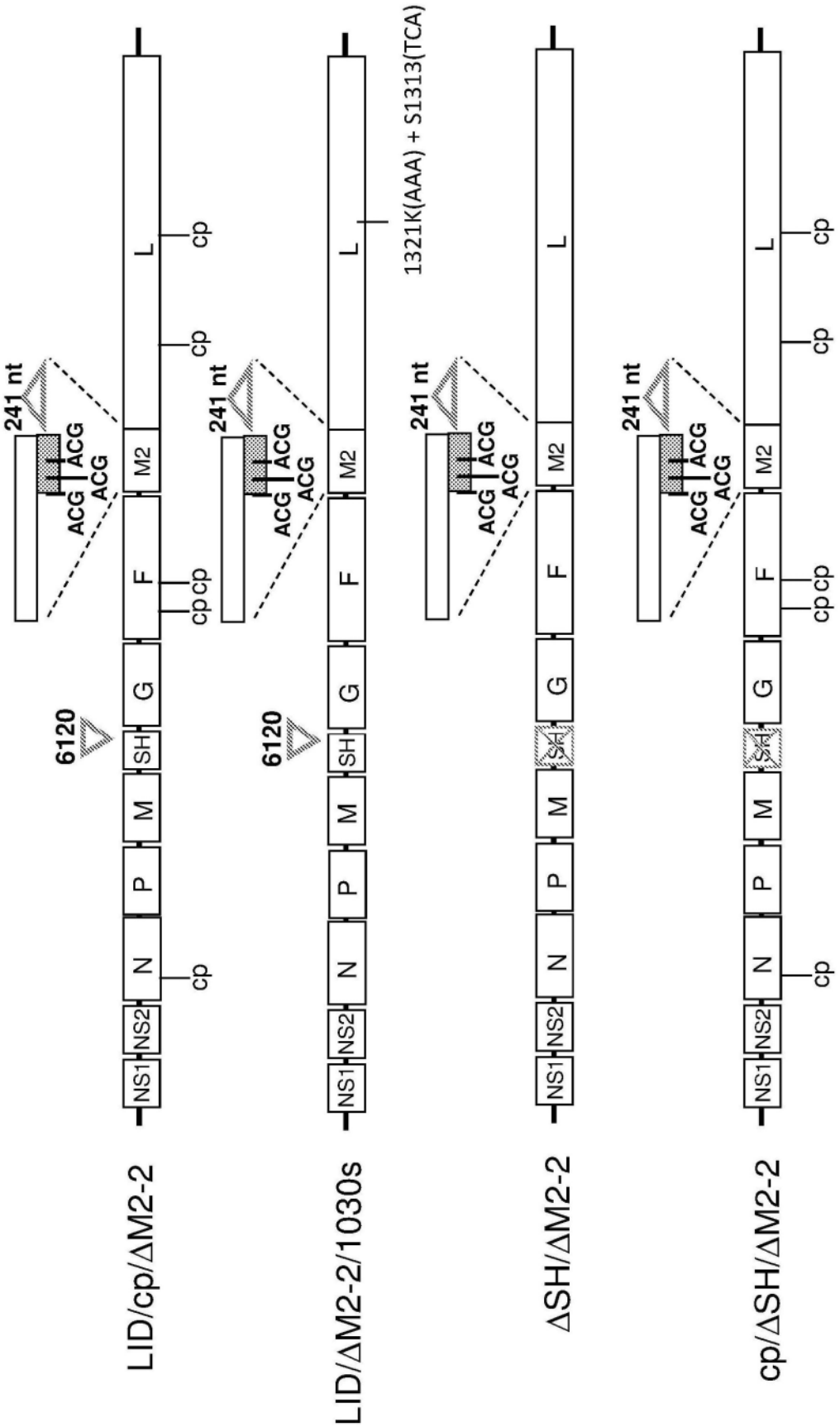
LID/cp/ΔM2-2
LID/ΔM2-2/1030s
ΔSH/ΔM2-2
cp/ΔSH/ΔM2-2
1321K(AAA) + S1313(TCA)
241 nt
ACG
ACG
ACG
6120
NS1
NS2
N
P
M
SH
G
F
M2
L
cp

图5

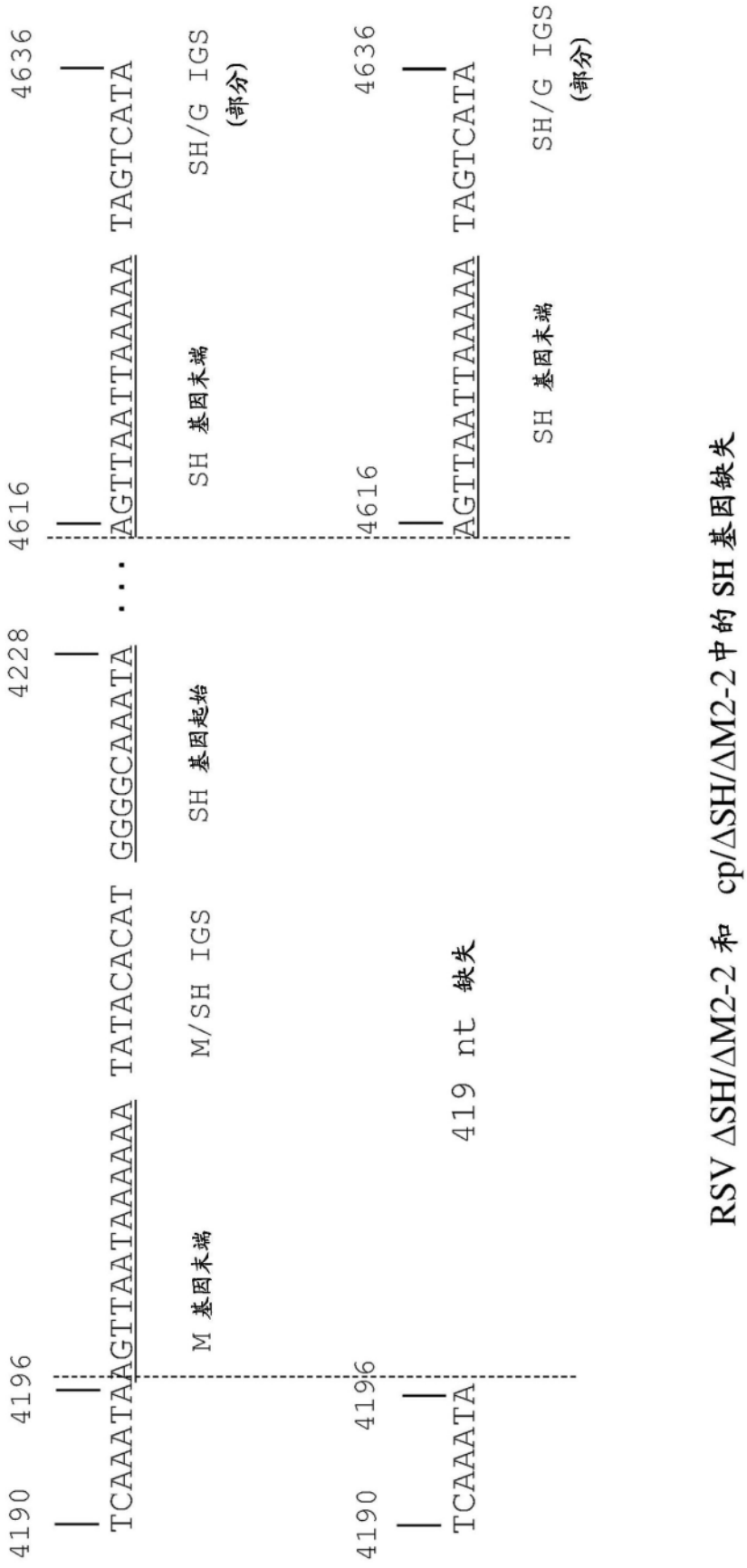
4190
4196
TCAAATA
AGTTAATAAAAAA
M 基因末端
TATACACAT
M/SH IGS
4228
GGGGCAAATA
SH 基因起始
4616
4636
AGTTAATTAAAAA
SH 基因末端
TAGTCATA
SH/G IGS
(部分)
419 nt 缺失
RSV ΔSH/ΔM2-2 和 cp/ΔSH/ΔM2-2 中的 SH 基因缺失

图6

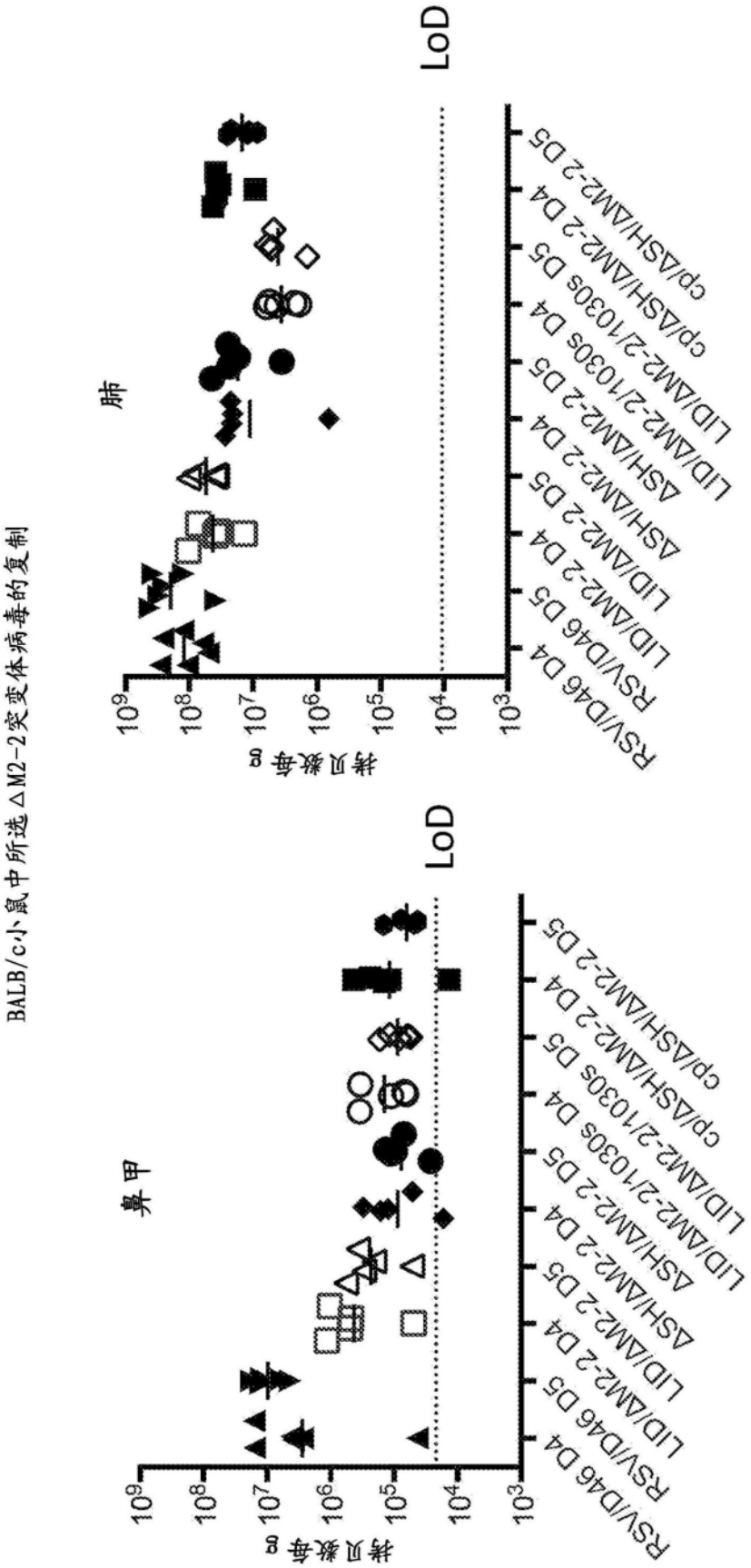
BALB/c小鼠中所选ΔM2-2突变体病毒的复制
鼻甲
肺
拷贝数每g
LoD
RSV/D46 D4
RSV/D46 D5
LID/ΔM2-2 D4
LID/ΔM2-2 D5
ASH/ΔM2-2 D4
ASH/ΔM2-2 D5
LID/ΔM2-2/1030S D4
LID/ΔM2-2/1030S D5
cp/ASH/ΔM2-2 D4
cp/ASH/ΔM2-2 D5

图7

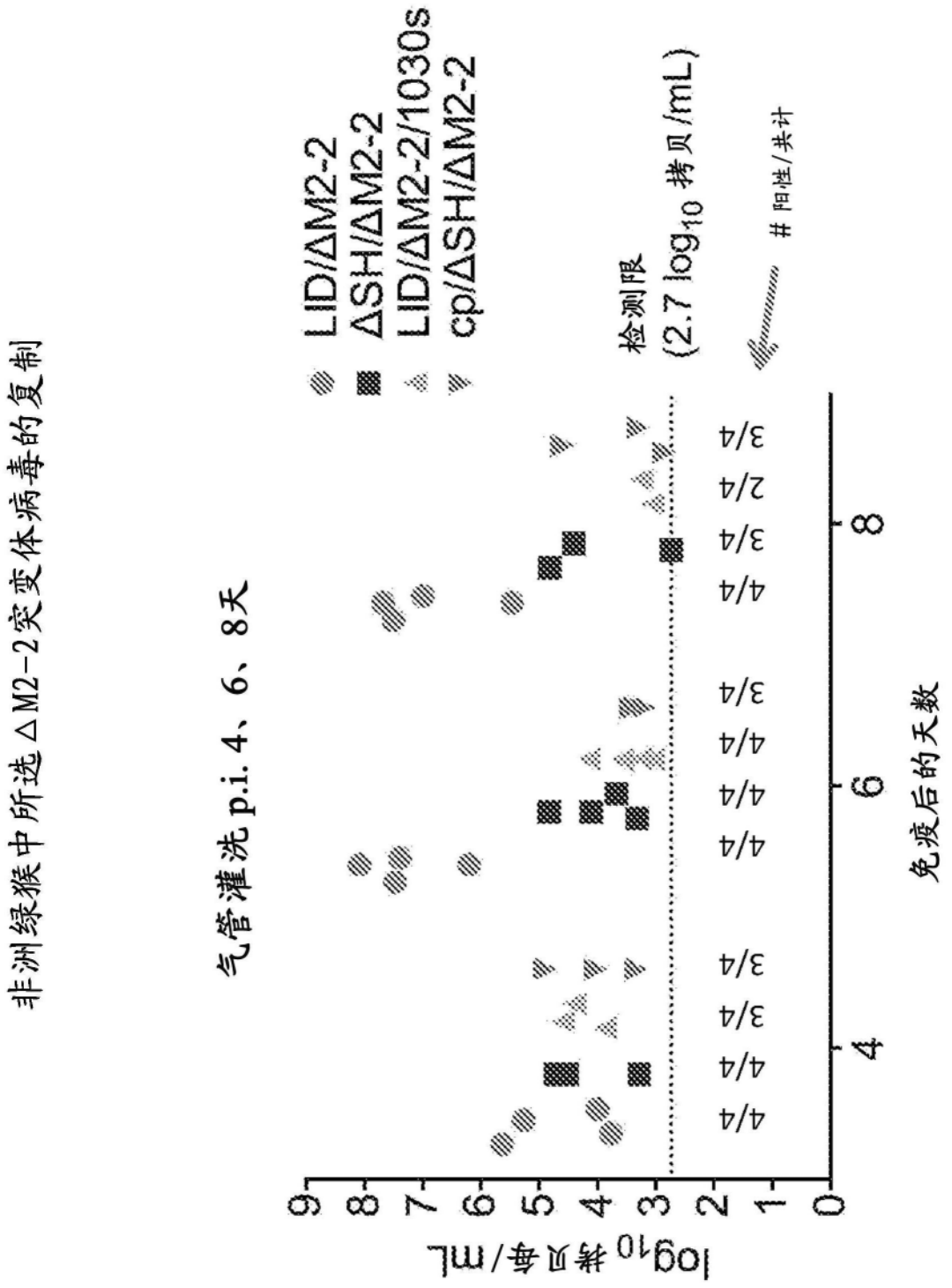
非洲绿猴中所选ΔM2-2突变体病毒的复制
气管灌洗 p.i. 4、6、8天
LID/ΔM2-2
ΔSH/ΔM2-2
LID/ΔM2-2/1030s
cp/ΔSH/ΔM2-2
检测限
(2.7 log10 拷贝/mL)
阳性/共计
log10 拷贝每/mL
免疫后的天数
4/4
4/4
3/4
3/4
4/4
4/4
4/4
3/4
4/4
3/4
2/4
3/4
4/4

图8A

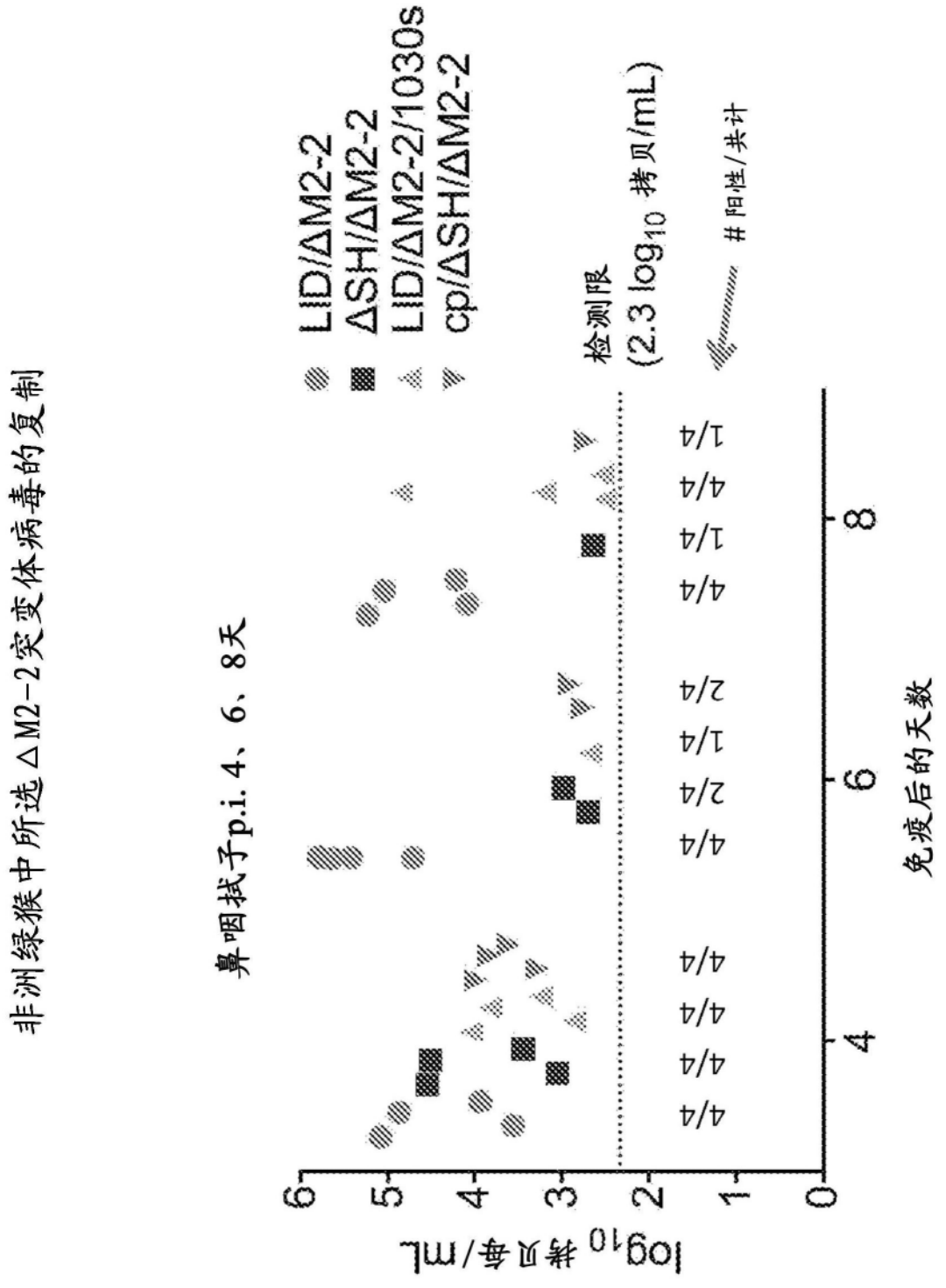
非洲绿猴中所选ΔM2-2突变体病毒的复制
鼻咽拭子p.i. 4、6、8天
LID/ΔM2-2
ΔSH/ΔM2-2
LID/ΔM2-2/1030s
cp/ΔSH/ΔM2-2
检测限
(2.3 log10 拷贝/mL)
阳性/共计
4/4
4/4
4/4
4/4
2/4
1/4
2/4
4/4
1/4
4/4
log10 拷贝每/mL
0
1
2
3
4
5
6
4
6
8
免疫后的天数

图8B

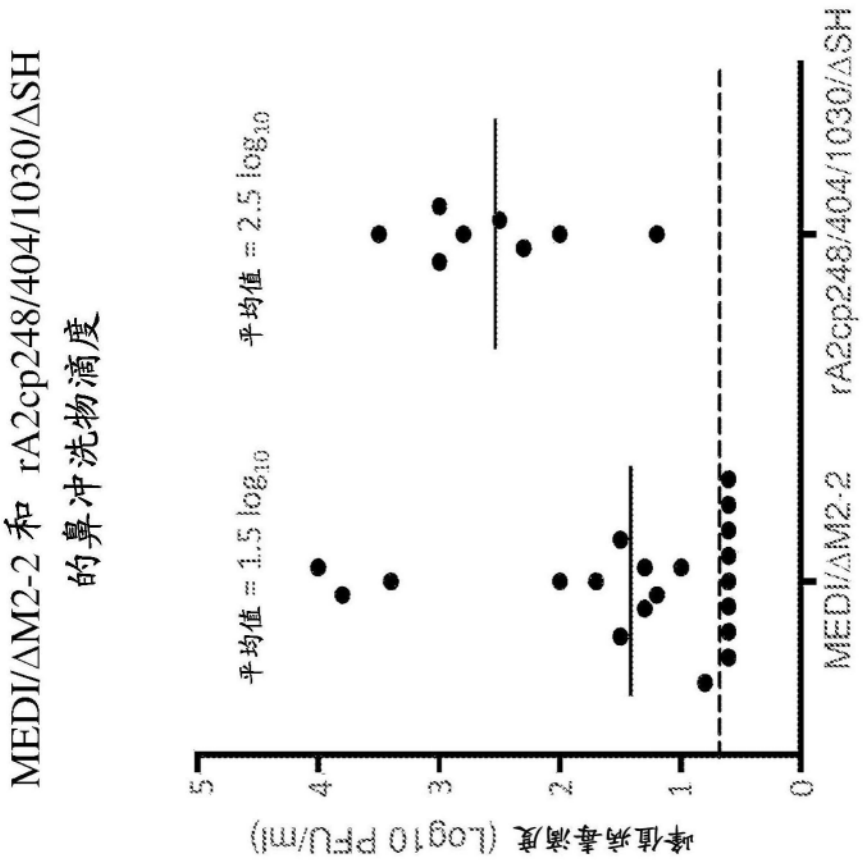
MEDI/ΔM2-2 和 rA2cp248/404/1030/ΔSH
的鼻冲洗物滴度
平均值 = 1.5 log10
平均值 = 2.5 log10
峰值病毒滴度 (Log10 PFU/ml)
5
4
3
2
1
0
MEDI/ΔM2-2
rA2cp248/404/1030/ΔSH

图9A

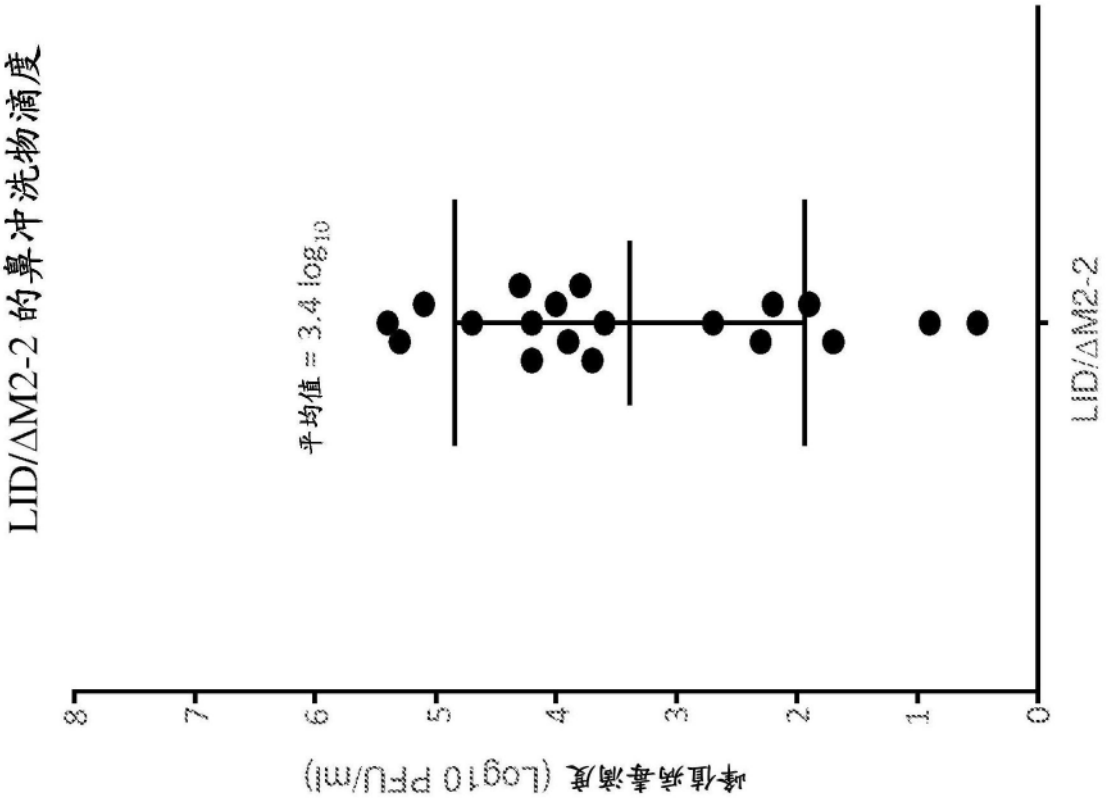
LID/ΔM2-2 的鼻冲洗物滴度
平均值 = 3.4 log10
峰值病毒滴度 (Log10 PFU/ml)
8
7
6
5
4
3
2
1
0
LID/ΔM2-2

图9B

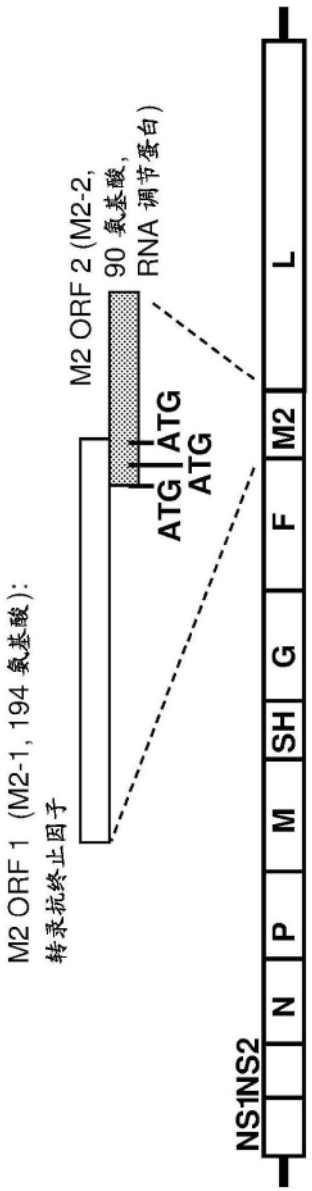
M2 ORF 1 (M2-1, 194 氨基酸):
转录抗终止因子
M2 ORF 2 (M2-2,
90 氨基酸,
RNA 调节蛋白)
ATG
ATG
ATG
NS1NS2
N
P
M
SH
G
F
M2
L

图10A

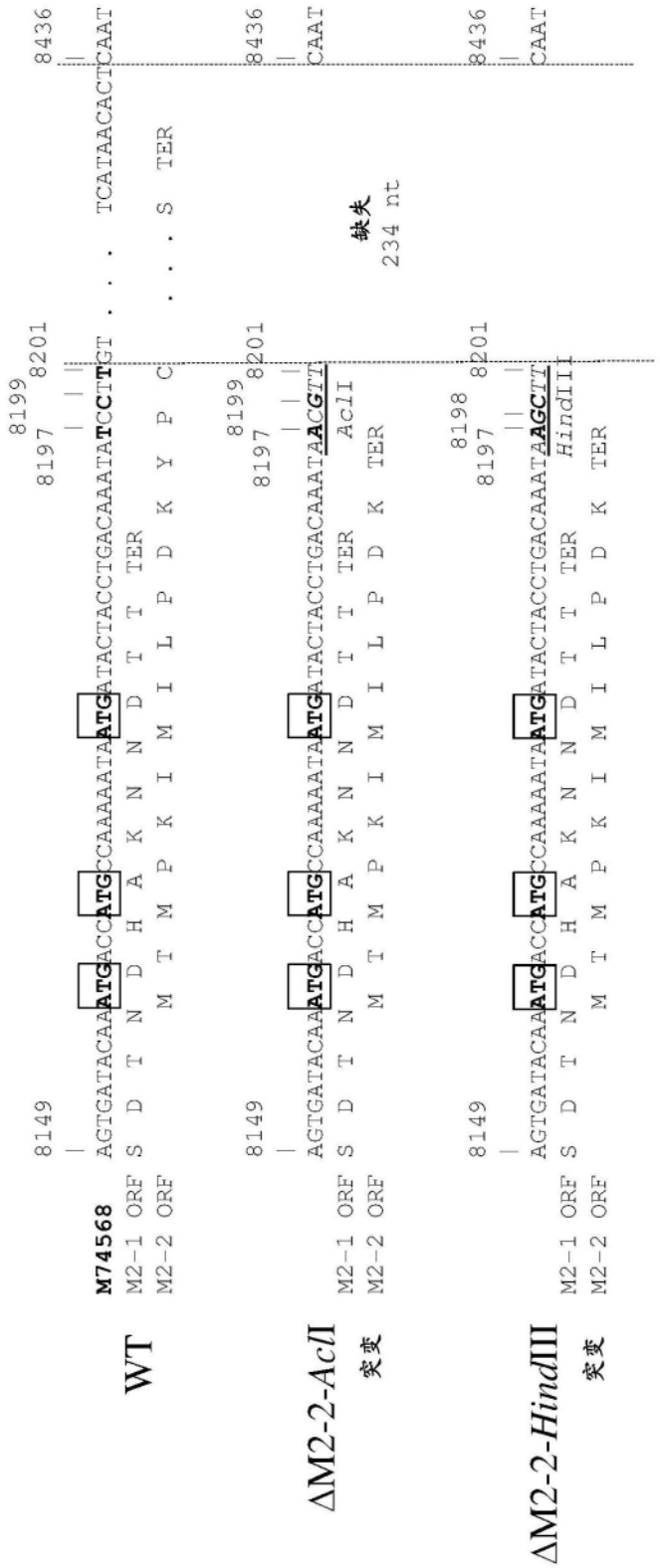
WT
M74568
M2-1 ORF
M2-2 ORF
ΔM2-2-AclI
突变
ΔM2-2-HindIII
突变
缺失
234 nt
AclI
HindIII
TER

图10B

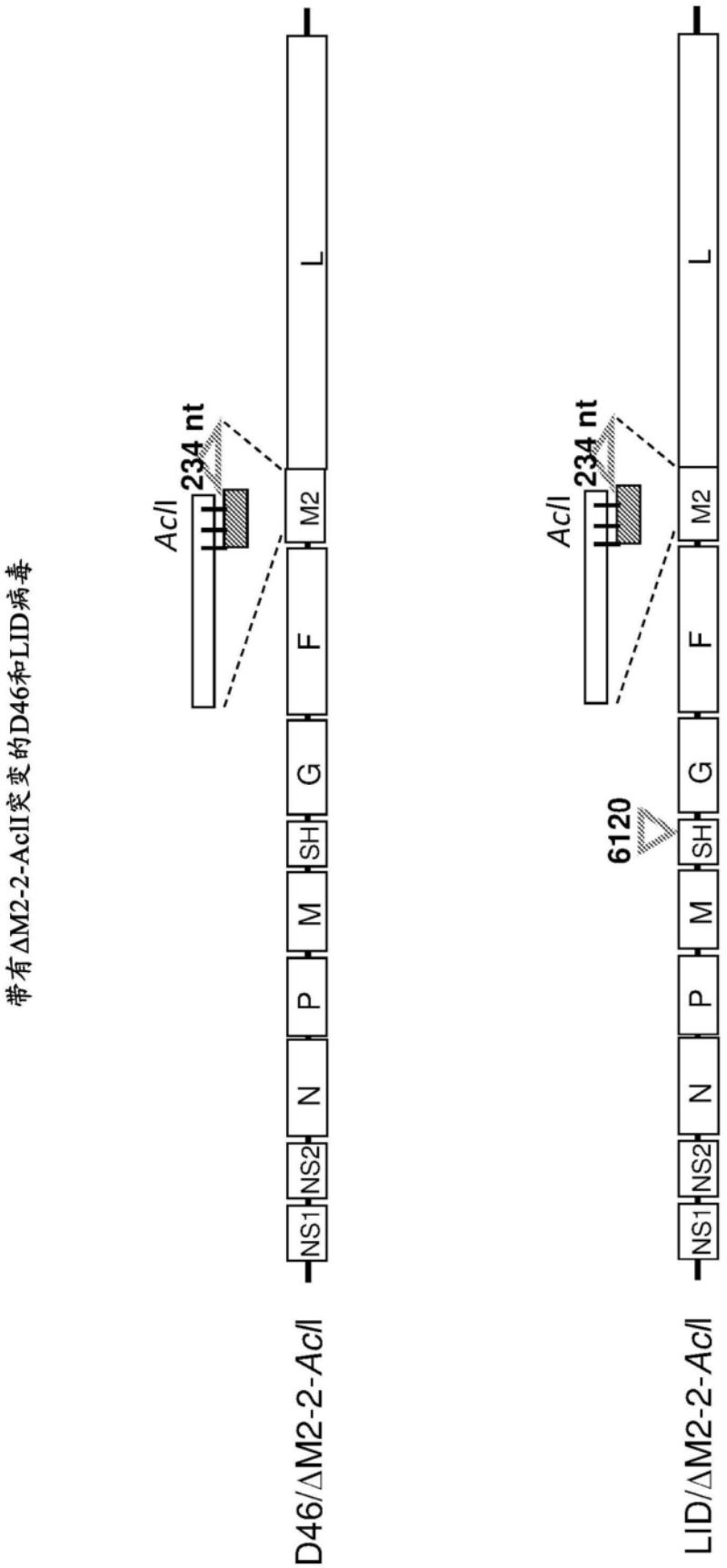
带有ΔM2-2-AclI突变的D46和LID病毒
AclI
234 nt
NS1
NS2
N
P
M
SH
G
F
M2
L
D46/ΔM2-2-AclI
AclI
234 nt
6120
NS1
NS2
N
P
M
SH
G
F
M2
L
LID/ΔM2-2-AclI

图11

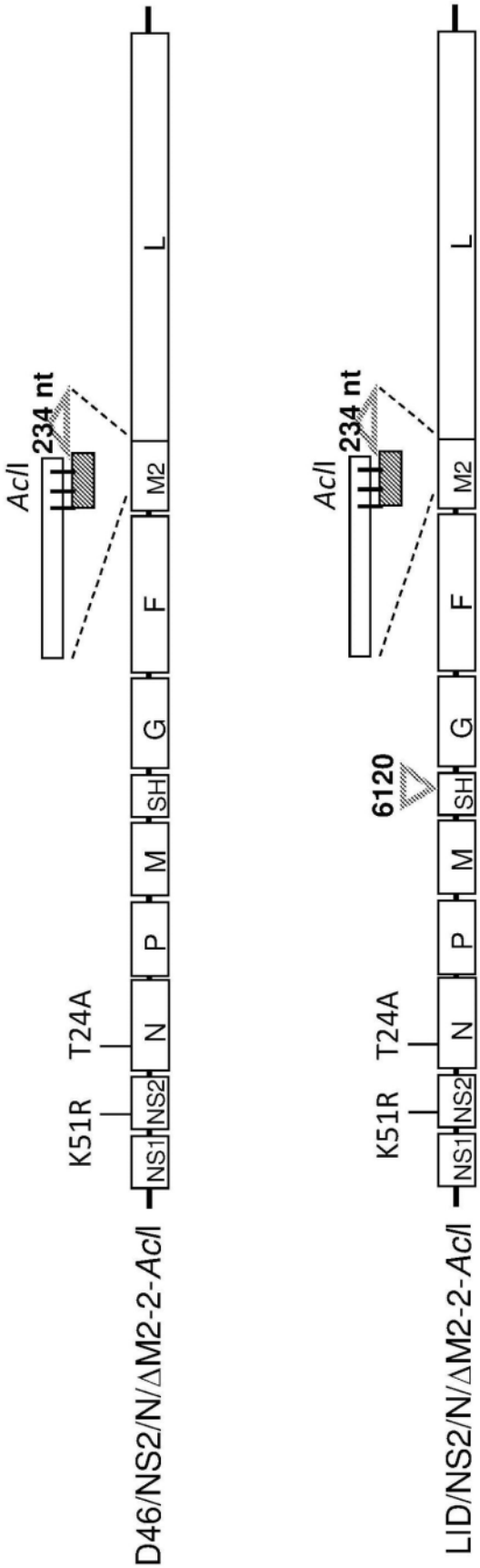
AclI
234 nt
L
M2
F
G
SH
M
P
N
T24A
NS2
K51R
NS1
D46/NS2/N/ΔM2-2-AclI
AclI
234 nt
L
M2
F
G
6120
SH
M
P
N
T24A
NS2
K51R
NS1
LID/NS2/N/ΔM2-2-AclI

图12A

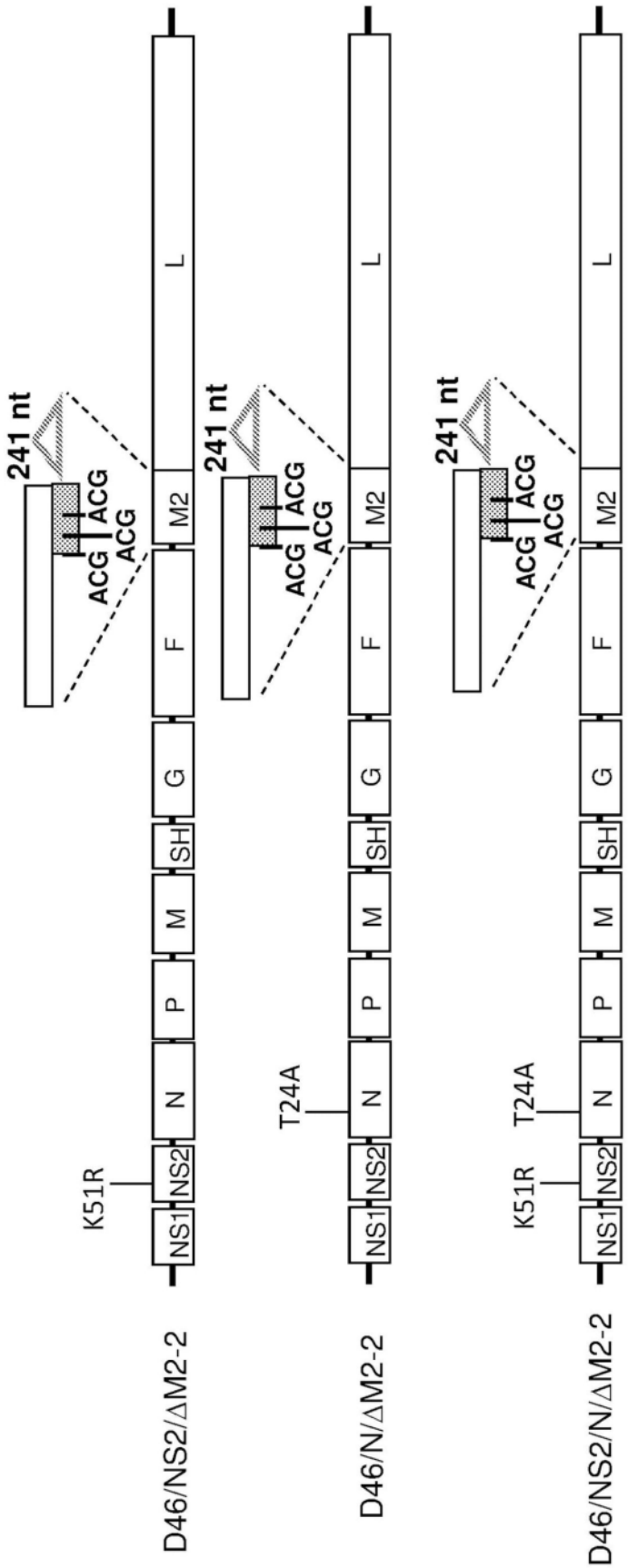
241 nt
ACG
ACG
M2
L
F
G
SH
M
P
N
NS2
NS1
K51R
D46/NS2/ΔM2-2
241 nt
ACG
ACG
M2
L
F
G
SH
M
P
N
T24A
NS1
NS2
D46/N/ΔM2-2
241 nt
ACG
ACG
M2
L
F
G
SH
M
P
N
T24A
K51R
NS1
NS2
D46/NS2/N/ΔM2-2

图12B

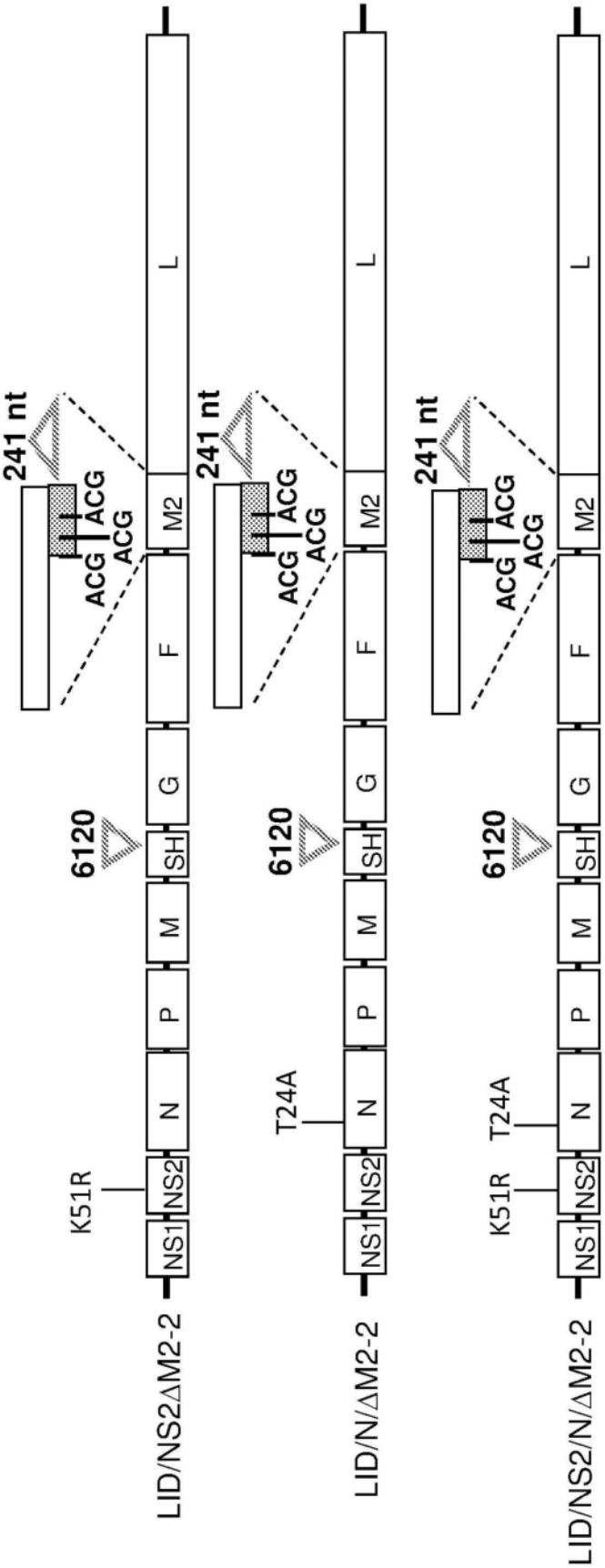
241 nt
ACG
ACG
ACG
6120
K51R
T24A
NS1
NS2
N
P
M
SH
G
F
M2
L
LID/NS2ΔM2-2
LID/N/ΔM2-2
LID/NS2/N/ΔM2-2

图12C

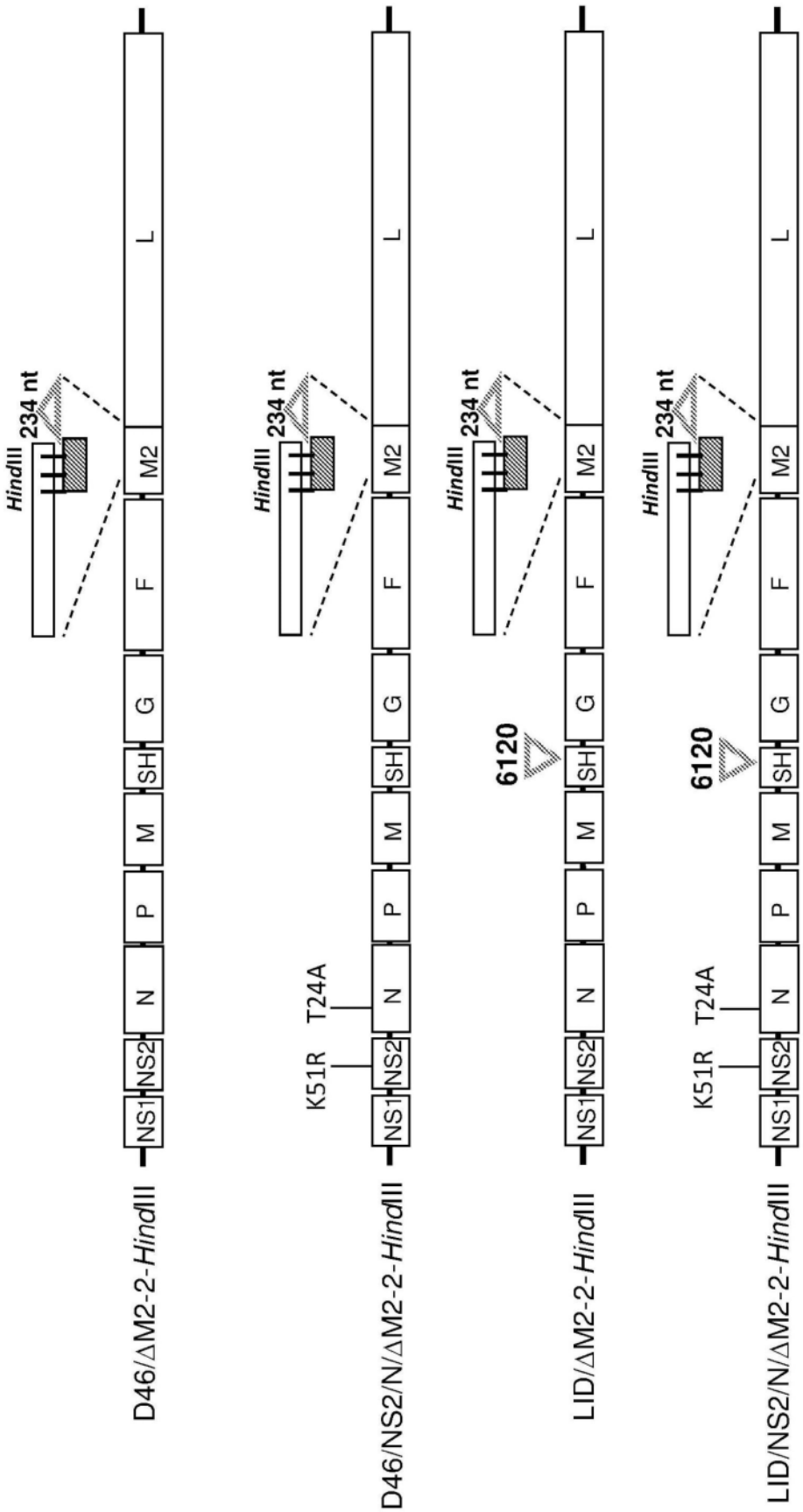
HindIII
234 nt
NS1
NS2
N
P
M
SH
G
F
M2
L
D46/ΔM2-2-HindIII
K51R
T24A
D46/NS2/N/ΔM2-2-HindIII
6120
LID/ΔM2-2-HindIII
LID/NS2/N/ΔM2-2-HindIII

图13

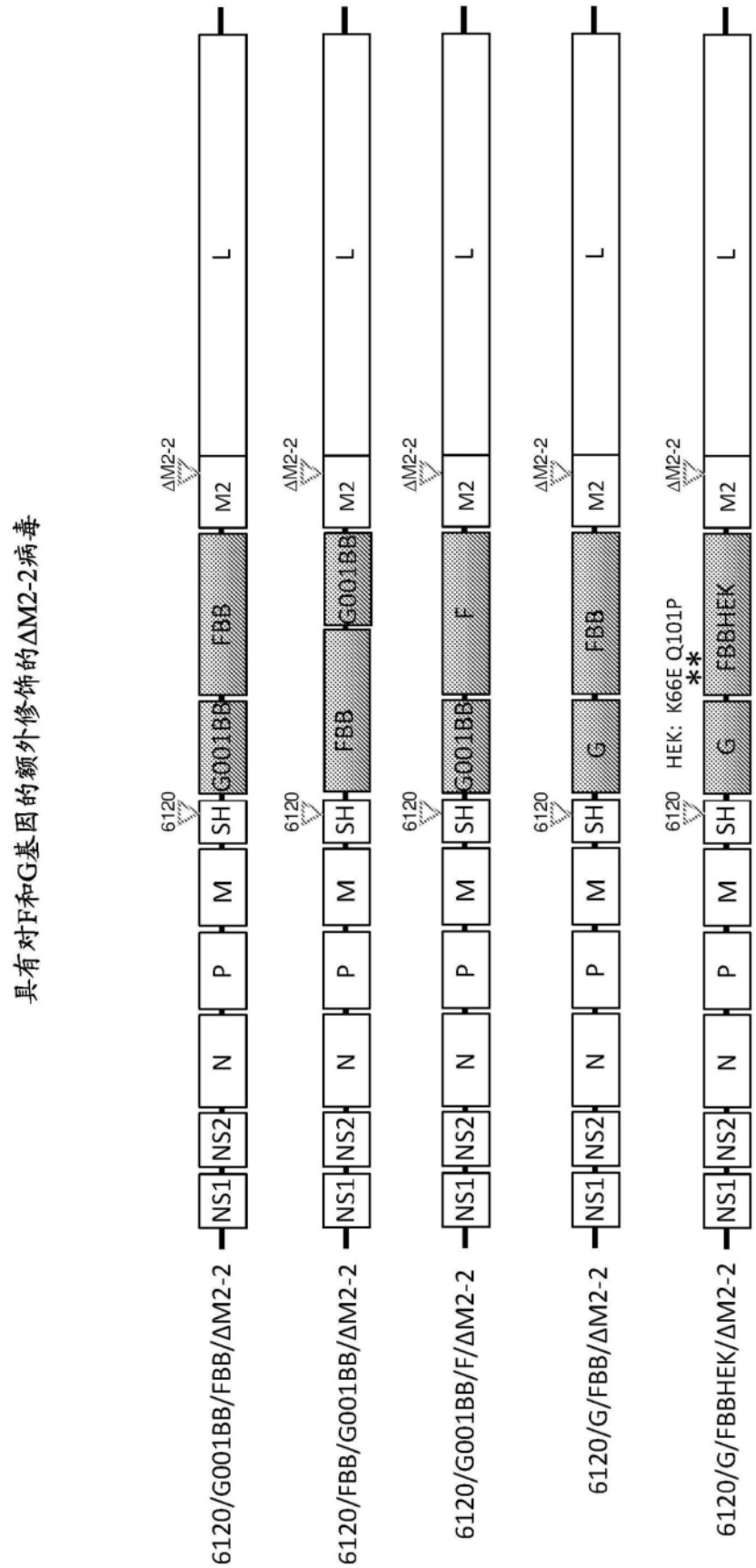
具有对F和G基因的额外修饰的ΔM2-2病毒
6120/G001BB/FBB/ΔM2-2
6120/FBB/G001BB/ΔM2-2
6120/G001BB/F/ΔM2-2
6120/G/FBB/ΔM2-2
6120/G/FBBHEK/ΔM2-2
NS1
NS2
N
P
M
SH
6120
G001BB
FBB
F
G
FBBHEK
M2
ΔM2-2
L
HEK: K66E Q101P
**

图14A

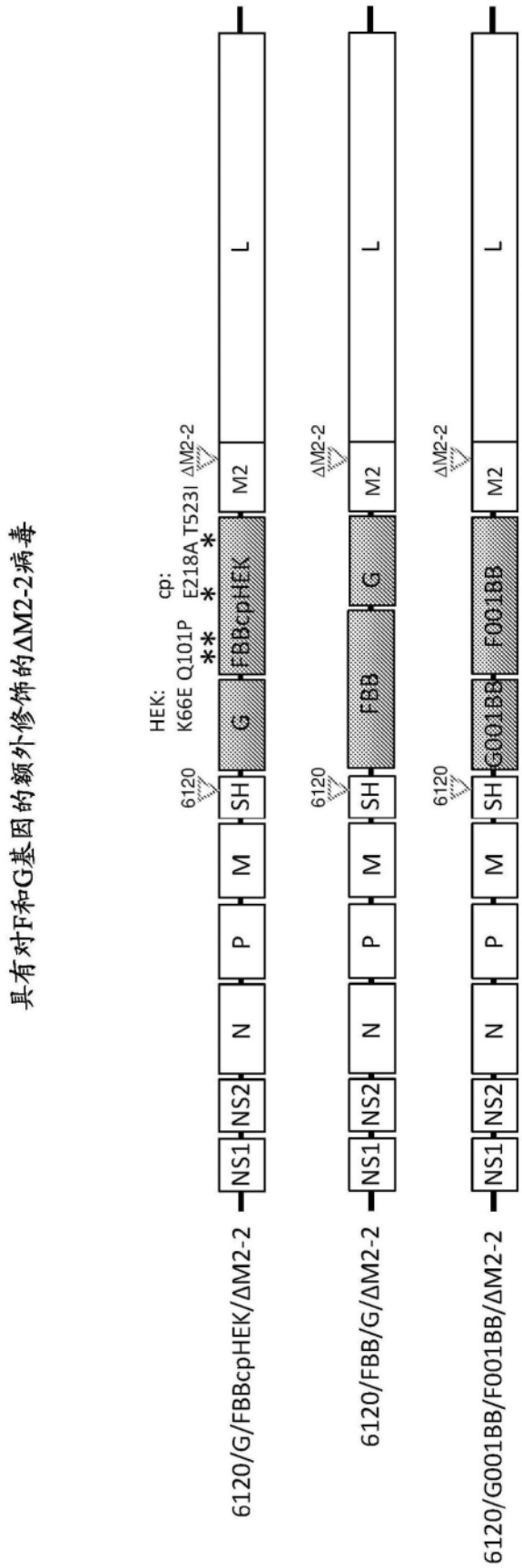
具有对F和G基因的额外修饰的ΔM2-2病毒
6120/G/FBBcpHEK/ΔM2-2
6120/FBB/G/ΔM2-2
6120/G001BB/F001BB/ΔM2-2
NS1
NS2
N
P
M
SH
G
FBBcpHEK
FBB
G001BB
F001BB
M2
L
6120
ΔM2-2
HEK:
K66E Q101P
cp:
E218A T523I

图14B

在32℃的P1病毒滴度和在32℃和37℃的P2病毒的比较

病毒	P1 滴度 pfu/ml 32℃	P2 滴度 pfu/ml 32℃ (MOI～0.01)	P2 滴度 pfu/ml 37℃ (MOI～0.01)
6120/G001BB/FBB/ΔM2-2	$1.7*10^7$	$1.95*10^7$	$2.35*10^7$
6120/FBB/G001BB/ΔM2-2	$3.25*10^7$	$3.1*10^7$	$3.3*10^7$
6120/G001BB/F/ΔM2-2	$6.66*10^6$	$4.8*10^7$	$3.65*10^7$
6120/G/FBB/ΔM2-2	$1.8*10^7$	$1.05*10^7$	$1.1*10^7$
6120/G/FBBHEK/ΔM2-2	$1.55*10^6$	$7.5*10^6$	$6.05*10^6$
6120/G/FBBcpHEK/ΔM2-2	$5.2*10^6$	$1.0*10^7$	$1.4*10^7$
6120/FBB/G/ΔM2-2	$2.5*10^7$	$6.5*10^6$	$6*10^6$
6120/G001BB/F001BB/ΔM2-2	$5.0*10^3$	$1.1*10^7$ (P3)	$1*10^7$ (P3)
wt LID	$2.1*10^7$	$5*10^6$	$1.4*10^7$
LID/ΔM2-2	$4.6*10^6$	$2.35*10^7$	$2*10^7$

具有对F和G基因的额外修饰的ΔM2-2病毒的病毒产量

图15

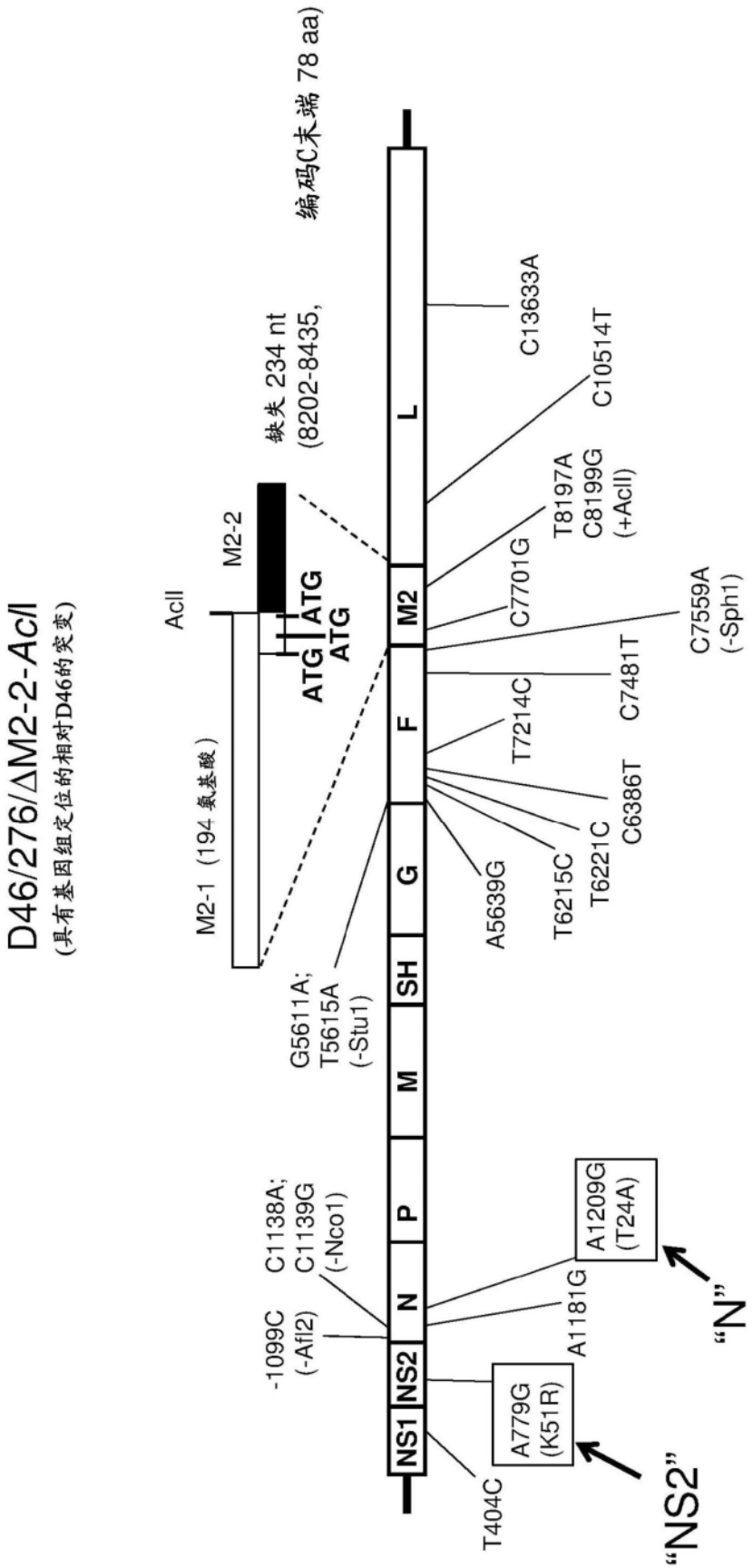
D46/276/ΔM2-2-AclI
(具有基因组定位的相对D46的突变)
AclI
M2-2
缺失 234 nt
(8202-8435,
编码C末端 78 aa)
M2-1 (194 氨基酸)
ATG
ATG
ATG
NS1
NS2
N
P
M
SH
G
F
M2
L
C13633A
C10514T
T8197A
C8199G
(+AclI)
C7701G
C7559A
(-Sph1)
C7481T
T7214C
C6386T
T6221C
T6215C
A5639G
G5611A;
T5615A
(-Stu1)
C1138A;
C1139G
(-Nco1)
-1099C
(-Afl2)
A1209G
(T24A)
A1181G
A779G
(K51R)
T404C
"N"
"NS2"

图16